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TUMORS OF THE BASAL GANGLIA *

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The purpose of this work was to investigate whether an analysis of the extrapyramidal syndromes as reported by various authors, particularly by Wilson,[1] Foerster,[2] von Monakow [3] and others, would be of any assistance in the diagnosis of a tumor arising in or invading the basal ganglia.

In order to make the study as nearly exact as possible, only those cases in the entire series have been selected in which the definite localization of the tumor has been verified by postmortem examination, the exact topography of a lesion often remaining obscure from the operative point of view alone. Since no particular histologic type of tumor originates specifically from the basal ganglia, it has been necessary to include as tumors of the basal ganglia not only the primary growths arising in them, but also the secondary ones which indirectly affected and destroyed this part of the brain. Though the tumors in this region have been found to be chiefly glioblastoma multiforme, the astrocytomas and unipolar spongioblastomas have also been met with.

Whether a tumor arising in or involving the basal ganglia may, by displacement, compression or destruction of the tissues, provoke irritative and paralytic symptoms analogous to those caused by tumors of the motor area, may best be determined by an analysis of the most important features of the syndromes that theoretically may be produced by a lesion situated in the corpus striatum, the thalamus, the subthalamus and the upper part of the mesencephalon.

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1. Wilson, S. A. K.: Progressive Lenticular Degeneration, in Lewandowsky: Handbuch der Neurologie, Berlin, Julius Springer, 1914, vol. 5, p. 951.

2. Foerster, O.: Zur Analyse und Pathophysiologie der striären Bewegung-Störungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:1, 1921.

3. von Monakow, C.: Recherches expérimentales et anatomo-pathologiques sur les connexions du corps strié et du noyau lenticulaire avec les autres parties du cerveau, Encéphale **20**:359, 1925; Schweiz. Arch. f. Neurol. u. Psychiat. **26**:225, 1925.

ANALYSIS OF SYNDROMES

1. *Corpus Striatum.*—(*a*) Syndrome of Excitation: The syndrome of excitation of the corpus striatum is still unknown. Wilson [4] has shown in experiments on monkeys that the corpus striatum cannot be stimulated electrically. The conclusion he has drawn in a later paper [5] may be of interest to note here:

> The fact that movement can be elicited experimentally from cerebellum, mesencephalon and optic thalamus respectively—all *via* extrapyramidal paths—but not from the corpus striatum, might be taken to suggest that the relation of the latter organ to the others may be one of superiority, conceivably on the analogy of frontal (psychomotor) in distinction from rolandic (motor) activity.

This is interesting in view of the fact that a study of the anatomic structure of the basal ganglia shows that the corpus striatum has mainly, if not exclusively, efferent fibers.

(*b*) Syndrome of Destruction: On the other hand, destruction of the corpus striatum causes a variety of syndromes. Anatomically, destructive lesions occur in a number of diseases, such as progressive lenticular degeneration of Wilson, multiple pseudosclerosis of Westphal-Strümpel, certain forms of torsion spasm of Thomalla-Wimmer, paralysis agitans, double athetosis etc. It is thus natural that one is tempted to consider any one of these diseases as being characteristic of a lesion of the corpus striatum. For example, one syndrome was described in 1911 by Vogt and Oppenheim,[6] and later another in 1912 by Wilson.[7] In 1921, Hall,[8] too, attempted to group under the name of hepatolenticular degeneration the several diseases that appeared to him to belong to the same morbid condition, that is, Wilson's disease, pseudosclerosis and torsion spasm.

2. *The Thalamus.*—(*a*) Syndrome of Excitation: Experiments on animals have shown that certain movements, probably postural in nature, may be elicited by electrical excitation of different parts of the thalamus. It is therefore probable that functions other than sensory and sensorial relays will be attributed in the future to the optic thalamus. In fact, this ganglion through its anatomic relationships is a part of the extrapyramidal system. In the lower animals, at least, its motor rôle is considerable.[9]

4. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427, 1914.

5. Wilson, S. A. K.: Modern Problems in Neurology, New York, William Wood & Company, 1929, p. 129.

6. Vogt, C., and Oppenheim, H.: Demonstration anatomischer Praeparate (Syndrome des Corpus striatum), Neurol. Centralbl. **30**:397, 1911.

7. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain **34**:295, 1912.

8. Hall, H. C.: La dégénérescence hépato-lenticulaire, maladie de Wilson, pseudosclérose, Paris, Masson & Cie, 1921.

9. Starling, E.: Principles of Human Physiology, Philadelphia, Lea & Febiger, 1915, p. 395.

In the light of present knowledge, the only manifestation of thalamic excitation that is useful to the clinician is pain. This typical painful sensation, which is deep, lancinating, paroxysmal and resistant to all kinds of analgesics, most often accompanies a syndrome of thalamic deficiency. But, as indicated by Lhermitte and Fumet,[10] it may also occur when there is no other sensory disturbance, thus giving a pure hemialgesic syndrome. It is perhaps proper to mention here the hyperesthesia to painful and thermic stimuli often observed in this condition.

(*b*) Syndrome of Destruction: If those manifestations are excluded that do not properly belong to the thalamic syndrome as described by Dejerine and his school,[11] but which are present when neighboring structures of the thalamus are involved, such as hemiplegia, asynergia and choreo-athetoid movements resulting from lesions of the internal capsule, cerebellar superior peduncles and extrapyramidal hypothalamic paths, the symptoms caused by destruction of the thalamus or of its single active area alone, the posterior part of the pulvinar, would be limited to the following: (1) hemianesthesia, particularly marked for deep sensation; (2) complete astereognosis; (3) hemiataxia in proportion to the degree of disturbance of the deep sensitivity; (4) characteristic pain.

But if one considers that an authentic thalamic syndrome may be present without the characteristic spontaneous pain, or without hyperesthesia for painful and thermic excitations, the identification of this syndrome becomes altogether impossible, since it then does not vary from the sensory disturbances which one may observe either in a pontile or cortical lesion of the sensory tract, the localizing diagnosis of which is always dependent on accompanying pathologic changes in the adjacent structures. Possibly, however, the fact that in the hemianesthesia of thalamic origin one finds occasionally a conservation of the perioral and periaboral sensibility (Foerster[12]) may be of significance in such diagnosis.

Furthermore, it is of interest to note the deficiency or loss of the movement of emotional expression, as evidenced by the spontaneous smile, on the opposite side of the face in certain cases of destructive lesion of the thalamus and lenticular nucleus. This dissociation of voluntary and emotional innervation in facial paresis of central origin was particularly well studied by Monrad-Krohn.[13]

10. Lhermitte, J., and Fumet, C.: Syndrome hémialgique pur d'origine thalamique chez un lacunaire, Rev. neurol. **37**:468, 1921.

11. Roussy, G.: La couche optique (étude anatomique, physiologique et clinique). Le syndrome thalamique, Thèse de Paris, 1907.

12. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls, Berlin, Urban & Schwarzenberg, 1927, p. 122.

13. Monrad-Krohn, G.: Dissociation of Voluntary and Emotional Innervation in Facial Paresis of Central Origin, Brain **47**:22, 1924.

Acute ulcers of the stomach [14] and circulatory disturbances in the liver [15] have also been produced experimentally in animals by destruction of the basal ganglia, chiefly the thalamus.

Finally, a good example, among others, of involuntary laughing and crying caused by a tumor located in the thalamus has been recorded by Weisenburg and Guilfoyle.[16]

3. *Subthalamus and Superior Mesencephalic Region.*—Although anatomists discriminate between these two regions, it seems more logical from a clinical standpoint to regard them as a pathway of tracts in which the gray structures, such as the corpus subthalamicum and the red nucleus, lie too close together not to be involved simultaneously in cases of gross lesions such as tumor.

(*a*) Syndrome of Excitation: The corpus subthalamicum or corpus of Luys receives an important number of striate fibers from the caudate nucleus through the ansa lenticularis. The destruction of the head of the caudate nucleus (Monokow [3]) or of the ansa lenticularis (Jakob,[17] Kashida [18]), where almost all the different optostriate paths converge, causes an almost total degeneration of the corpus of Luys. The latter is therefore an extrapyramidal relay between the nucleus caudatus and the red nucleus. Karplus and Kreidl [19] have demonstrated in animals the existence of a sympathetic center in the corpus of Luys, excitation of which provoked an ipsolateral hyperthermia, hemihidrosis, flushing of the skin, mydriasis and exophthalmos. The presence of a simliar center in man has never been definitely proved. It is true that among other symptoms a vasomotor flush and a free perspiration of the face commonly occur as a result of an acute dilatation of the third ventricle. For example, such symptoms were recently observed by myself in a patient with a cerebellar cyst in whom paroxysmal headache due to a

14. Oberling, C., and Kallo, A.: Ulcères aigus de l'estomac consécutifs à des lésions expérimentales des noyaux gris centraux, Compt. rend. Soc. de biol. **102:** 832, 1929.

15. Oberling, C., and Kallo, A.: Troubles circulatoires du foie consécutifs à des lésions expérimentales des noyaux gris centraux, Compt. rend. Soc. de biol. **102:**916, 1929.

16. Weisenburg, T., and Guilfoyle, W.: Tumour Destroying Most of One Optic Thalamus and Causing Central Pains, Vasomotor and Trophic Disturbances, Involuntary Howling and Deviation of the Body to the Opposite Side, Rev. Neurol. & Psychiat. **8:**325, 1910.

17. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923.

18. Kashida: Ueber Gehirnarteriosclerose des früheren Alters und über die Kombination von corticalen pyramidalen und extrapyramidalen Symptomen bei der Gehirnarteriosclerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **94:**659, 1925.

19. Karplus, J., and Kreidl, A.: Gehirn und Sympathicus, Arch. f. d. ges. Physiol. **171:**192, 1918.

transitory obstruction of the iter was always accompanied by hypothalamic manifestations. These phenomena could, however, be explained apart from the participation of the hypothetic center of the corpus subthalamicum, since they are ordinarily attributed to other sympathetic centers in the floor of the third ventricle.

The excitation phenomena of the red nucleus are better known. Graham Brown [20] has found that unilateral excitation of the red nucleus provokes:

> . . . a state of flexion in the arm of the same side and a state of extension in the arm of the opposite side. On cessation of stimulation, these reactions are continued as maintained posture. These movements of the arms are accompanied by movements of other parts of the body. The tail seems to bend to the same side, the lower limb of the same side extends, while that of the opposite side flexes, the head is rotated in such a manner that the face is turned away from the side stimulated.

(*b*) Syndrome of Destruction: Another reason for not discriminating between the subthalamus and the region of the red nucleus lies in the fact that any destructive lesion of this area of the brain may lead to tremor and to involuntary movement. As already noted, Dejerine has mentioned choreo-athetoid movements as being a frequent, if not a constant, element of the thalamic syndrome.

However, in pathologic conditions the involuntary movements cannot be explained by the involvement of the thalamus alone. Although the latter functions as a relay for the cerebellothalamic fibers, a number of observations verified by anatomic studies (Vincent,[21] Conos,[22] Long,[23] et al.) favor the hypothesis that there is a concomitant subthalamic lesion. In fact, Guillain and Alajouanine [24] also described a pure hypothalamic syndrome caused by destructive lesions situated below the thalamus and involving simultaneously the pyramidal tract, the mesial filet, the paths of the superior cerebellar peduncle and certain extrapyramidal radiations. According to these authors, this syndrome is made up of: (1) a slight hemiparesis, often occurring without the sign of Babinski; (2) involuntary athetoid movements with a special position of the hand; (3) objective sensory disturbances evidenced by a hemianesthesia involving

20. Brown, G.: On the Effect of Artificial Stimulation of the Red Nucleus in the Anthropoid Ape, J. Physiol. **49**:185, 1915.

21. Vincent, C.: Syndrome thalamique avec troubles cérébelleux et vaso-asymétrie, Rev. neurol. **16**:553, 1908.

22. Conos, B.: Un cas de syndrome thalamique de Dejerine avec hémianopsie et troubles cérébelleux légers, Encéphale **1**:468, 1909.

23. Long, E.: Deux observations anatomo-cliniques de syndrome thalamique, Rev. neurol. **18**:197, 1910.

24. Guillain, G., and Alajouanine, T.: Études neurologiques. Syndrome du carrefour hypothalamique, Paris, Masson & Cie, 1930.

predominantly the deep sensibility and particularly stereognosis, but without subjective disturbances and without spontaneous pains; (4) cerebellar disturbances, chiefly related to synergia and tonus, while balance is little disturbed, and (5) a complete or incomplete lateral homonymous hemianopia.

A third well known syndrome of this region is the classic one of Benedict. In this clinical picture a lesion of the red nucleus was, with or without sufficient justification, regarded as the cause of the hemichorea or hemitremor observed on the same side as the hemianesthesia. Souques, Crouzon and Bertrand [25] have recently brought forward new data supporting the theory that attributes involuntary movements to lesions limited to the red nucleus. That the red nucleus, however, is in all probability not the only structure responsible for these manifestations would appear from other studies [26] which conclude that this nucleus is one of the centers for tonus and certain standing and postural reflexes.

Laboratory observations on decerebrate rigidity have shown that tonic fits apparently result from lesions of an acute nature in the neighborhood of the iter, extending to the red nucleus. Graham Brown,[27] for example, has even developed the hypothesis, based on a wealth of experiment, that the postural reflexes that make up decerebrate rigidity have their center in the activity of the red nucleus. As a matter of fact, although decerebrate rigidity is not abolished when the red nucleus is destroyed in decerebrate animals, nevertheless tonic disturbances are provoked on the opposite side of the body as detected by myographic examination (Cobb, Bailey and Holtz [28]).

Without going into the details of these modern controversial hypotheses, it is nevertheless of interest to consider in addition the conception that the involuntary movements noted in all of these syndromes are thought to result from a destruction of the corpus of Luys. Balthazar [29] reviewed the literature on this question and has reported a personal observation in which he attempted to prove that the elective destruction of the corpus subthalamicum resulted in a syndrome characterized by

25. Souques, A.; Crouzon, O., and Bertrand, I.: Révision du syndrome de Benedict à propos de l'autopsie d'un cas de ce syndrome. Forme trémo-choréo-athétoide et hypertonique du syndrome du noyau rouge, Rev. neurol. **2**:377, 1930.

26. Brown, G.: Postural and Non-Postural Activities of the Midbrain, Proc. Roy. Soc. London, s. B., **87**:145, 1914. Magnus, R.: Beiträge zum Problem der Körper-Stellung, Arch. f. d. ges. Physiol. **163**:405, 1916.

27. Brown (footnote 26).

28. Cobb, S.; Bailey, A., and Holtz, P.: On the Genesis and Inhibition of Extensor Rigidity, Am. J. Physiol. **44**:239, 1917.

29. Balthazar, K.: Ueber das Syndrom des Corpus Luys am Hand eines anatomisch untersuchten Falles von Hemiballismus, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:702, 1930.

hemiballism. Lafora,[30] in fact, produced choreo-athetoid movements in cats by means of lesions of the subthalamus and superior cerebellar peduncle.

Whether the source of involuntary movements and tremors lies in the corpus of Luys, the ansa lenticularis, in the tail of the caudate nucleus, which likewise has its termination in the hypothalamic region, or in the closely adjacent substantia nigra does not pertain to this study. But what is of importance is the possible appearance of tremor and choreo-athetoid movements in the evolution of a tumor of this region. Moreover, even the quality of the tremor is of no great importance. Apparently, too many exceptions contradict the accepted theories. Indeed, if the tremor in these patients is ordinarily slow and a rest tremor, as in the extrapyramidal diseases, it also can be wholly intentional. Thus, in a case that I observed in Penfield's clinic, a tumor of the thalamus provoked a typical intentional tremor comparable to that noted in disseminated sclerosis in which this symptom is generally attributed to a lesion in the superior cerebellar peduncles.

If one adds to the foregoing, first, the palsy of the conjugate elevation of the eye which ordinarily characterizes a lesion of the posterior bundle in the region of the corpora quadrigemina, but which occasionally occurs in the hypothalamic disorders (Dereux[31]), and second, respiratory troubles due to a lesion of the respiratory tract described by Graham Brown[32] in the neighborhood of the corpus subthalamicum, the so-called symptomatology of the tumor of the basal ganglia, will, I think, be completed.

It will now be shown how little these theoretical data are confirmed by clinical observations.

CLINICAL OBSERVATIONS

GROUP 1.—This group of cases illustrates apparently specific symptoms of a lesion of the basal ganglia (five cases).

CASE 1.—*Choreo-athetoid movements. Attacks of rigidity. Disease of six weeks' duration. Puncture of ventricle without results. Autopsy: Glioblastoma multiforme of the third ventricle, involving the basal ganglia and compressing the iter. Acute hydrocephalus.*

History.—Lillian P., 3½ years of age, was admitted to the Johns Hopkins Hospital on March 11, 1912. For some time before definite symptoms began, the

30. Lafora, G.: Libro en honor de S. Ramón y Cajal, Madrid, Jiménez y Molina, 1922, vol. 2, p. 261.

31. Dereux, J.: Le syndrome de Parinaud (étiologie, anatomie pathologique), Médecine **11**:146, 1930.

32. Brown, G.: Note on the Physiology of the Basal Ganglia and Midbrain of the Anthropoid Ape, Especially in Reference to the Act of Laughter, J. Physiol. **49**:195, 1915; A Respiratory Tract in the Mid-Brain, Proc. Physiol. Soc. London, 1914, p. xxxii.

child was observed to tire easily, retiring from play with her mates to sit and watch them. She had always been precocious, singing at an early age, and reciting poetry. About five weeks before she was admitted to the hospital, the first definite symptoms appeared in movements and contractions of the right hand, apparently associated with an acute febrile attack. The child would approach and touch a person with her hand and quickly withdraw it, repeating the motion over and over. A few days later, she began to drag the right foot in walking. Within the first week, she began to have strange mental symptoms, standing in a corner, talking queerly, wandering around and failing to recognize any one. On finishing a meal she would continue motions used while eating. After admission to the hospital she lay without speaking, paying no attention to surroundings. Contractions came on at frequent intervals. Movements involved both sides, but contractions only the right. The mother thought that the child could see nothing at times. She had eaten nothing voluntarily for two weeks. She had had no sphincter control for two weeks. The bowels were very costive.

First Physical Examination—March 11, 1912: Examination of the eyegrounds was difficult on account of lateral movements of the eyeballs, which were practically constant during the examination. The impression was gained that the swelling of the left disk was greater than on the right side, though no measurements could be made. The vessels were sharply defined. There was apparently no vision. The pupils did not react to light. The right corner of the mouth was a little lower than the left. The patient lay with both legs flexed, the left being kept in a position of external rotation of the thigh, flexion of the knee and extension of the great toe. The other toes were in plantar flexion. When aroused, she made thrashing movements of both arms with the left kept flexed at the elbow and wrist. Movements of the left hand were decidedly athetoid. There were occasional chewing movements of the jaw and lips, with retraction of the corner of the mouth toward the left side. There was no stiffness of the neck.

Second Examination.—March 11: The patient was stuporous and the eyes were staring. There was marked exaggeration of the knee jerks, greater on the left. There was patellar and ankle clonus. Any strong stimulatory movement was followed by curious swimming movements of the arms and legs. The left leg was moved about in an involuntary manner. The right leg was held stiff, with the sole of the foot inverted and the great toe extended. At times the left leg could be manipulated; at other times it was rigidly contracted in extension. Plantar stimulation of the right foot caused drawing away of the leg and a sudden increase in the permanent extension of the great toe, followed by a maintained plantar flexion of all the toes.

Third Examination.—March 11: The right hand was flexed at the elbow and at the wrist. Noise, such as clapping the hands, did not seem to cause any response, but if the patient was touched anywhere she was apt to extend the leg, jerk the arms and roll the head.

Course.—March 12: The patient tended to keep the head turned to the left shoulder, and on straightening, the head sometimes returned to this position. On watching movements closely, one saw a tendency to continuance in march, the first motion always being pronation of the left forearm, then flexion of the wrist and strong flexion of the left knee, followed by extension and rest. The patient was unable to record any new impression, and comprehension was absent.

The eyes were held to the right most of the time, but occasionally rolled to the left. There was no weakness of any of the extra-ocular muscles. The pupils were normal. Both disks were definitely edematous; there was an advancing choked

disk. The patient had vomited several times. Movements of the right hand resembled an athetoid type, while those of the left resembled a choreiform type.

March 14: The pulse, in rate from 58 to 72, was quite irregular. The lungs were clear. There was difficulty in swallowing.

March 15: Both arms were held rigid. The right leg was much less rigid. Lumbar puncture revealed: pressure, 500; milky-white fluid; sediment nearly all polymorphonuclear cells; cultures showed no growth; there were no tubercle bacilli.

Impression: The impression was that the condition was cerebrospinal meningitis. Flexner antimeningitis serum was introduced into the spinal canal.

March 16: The patient was unable to swallow. There was a tendency to convulsive movements. There was less tonicity in the two arms. Respiration had become more irregular and the pulse more rapid. The serum injection seemed to have aggravated the condition.

March 18: The ventricle was tapped by Dr. Cushing. A slightly cloudy fluid was obtained (8 cc.); it was not under great pressure; it showed slight sediment, only 2 or 3 leukocytes. Respiration and pulse were irregular.

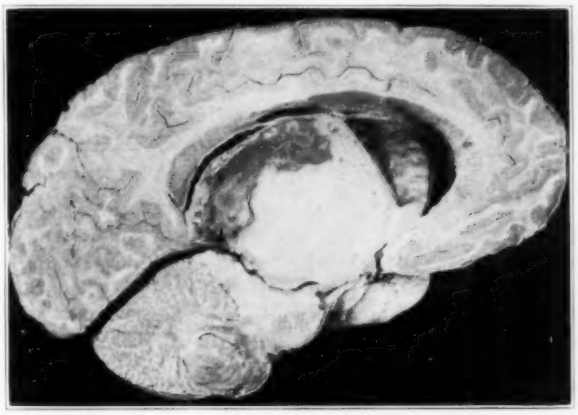

Fig. 1 (case 1).—Midsection showing a glioma lying in the region of the basal ganglia, compressing the pons and iter, and provoking hydrocephalus and a mesencephalic functional transection. The patient presented choreo-athetoid movements and attacks of rigidity.

March 19: No relief followed the puncture of ventricle. Death occurred.

Diagnosis.—The successive diagnoses were (1) encephalitis, (2) rapidly growing tumor, (3) cerebrospinal meningitis and (4) tuberculous meningitis.

Autopsy.—A large tumor (a highly malignant unclassified glioma with abundant mitoses) lay in the region of the basal ganglia and evidently connected them. It was above the pons and above the iter, which, however, must have become markedly compressed, for there was a high grade internal hydrocephalus, involving particularly the third ventricle. There had been no hemorrhage into this ventricle. There was no evidence whatsoever of infection (fig. 1).

CASE 2.—*Rigidity. Tremor. Left hemiparesis and hemihypesthesia. Tonic and clonic convulsions. Rapid increase of symptoms. Negative exploration. Death. Autopsy: Spongioblastoma polare.*

History.—Vincent B., aged 3½ years, was admitted to the Peter Bent Brigham Hospital on March 8, 1926. He had always been healthy before the present illness.

In June, 1925, nine months before admission to the hospital, he began to drag the left foot slightly. In July, he was unable to use the left arm as well as formerly. In December, he began vomiting once or twice every second or third day, and this continued to the time of admission. About the same time he began complaining of headaches, first occipital, now frontal. Since then there had also been urinary incontinence. The weakness of the left extremities continued to progress until there was a slight but definite spasticity in the left arm and left leg. Left internal strabismus developed. The child became exceedingly fretful and quite stuporous at times.

Fig. 2 (case 2).—Characteristic attitude of decerebration. The child lies stiffened out with the head tilted to the left, the right arm flexed and the left extended. Both hands are flexed at wrist and fingers closed over thumb in palm. The left leg is flexed in contralateral position to the arm and to the head.

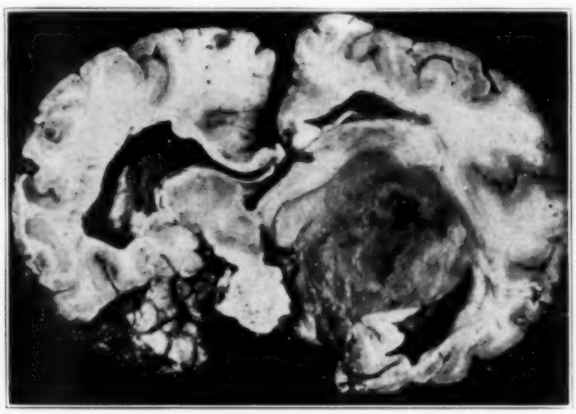

Fig. 3 (case 2).—A large spongioblastoma in the right hemisphere involving the region of the basal ganglia. The patient presented rigidity and tremor, left hemiparesis and hemihypesthesia, tonic and clonic convulsions.

Physical Examination.—March 11, 1926: There was definite paresis with spasticity of the left arm and left leg. The child was rather drowsy. The head was enlarged, and a cracked-pot sound could be elicited. The neck was definitely stiff. Both eyes showed a choked disk of 3 diopters, with beginning secondary atrophy. The pupils were normal and reacted to light. There was paresis of the left external rectus and weakness of the left side of the face, particularly in motion. There seemed to be definite hypesthesia of the entire left side of the body, without hypesthesia of the face. The Babinski sign was positive on the left.

Operation.—March 17: A right cerebral exploration was made for a presumed tumor. Internal hydrocephalus was found.

Ventriculogram.—Dilated ventricles were shown, with no lateral displacement or deformity except that the ventricles appeared humped as if by a suprasellar tumor. The air passed freely from side to side.

Postoperative Course.—March 17: A generalized convulsion occurred, with rotation of the eyes upward, stiffening of the left extremities, and clonic convulsions of the right arm. A lumbar puncture needle was introduced into the ventricle and considerable air and 50 cc. of fluid removed. The patient was more responsive afterward.

March 18: There was irregular breathing. The child lay stiffened out, with both legs in an equinovarus position, the left one being extremely spastic. Both arms were also stiff, with the hands flexed at the wrist and the fingers closed over the thumbs in the palm (fig. 2). The eyes were almost constantly deviated conjugately to the right.

March 22: Spontaneous nystagmus was present when the child happened to look to either side. He held the extremities rigid.

March 26: The child continued to be stiff and the tremors continued.

April 10: Rigidity was so great that the child could be handled by one leg or arm almost like an unjointed rod.

Autopsy.—There was a large spongioblastoma of the right hemisphere, involving the region of the basal ganglia. The right thalamus was flattened out to a thin band along the distorted third ventricle. The corpus striatum and the internal capsule were totally destroyed (fig. 3).

CASE 3.—*Rigidity of the left arm. Marked intention tremor of the left arm and leg. Left hemiparesis. Clonic convulsions. Partial removal of a tumor and repeated evacuation of a cyst. Survival period of four years. Death. Autopsy: Astrocytoma protoplasmaticum.*

History.—Esther W., aged 9, was admitted to the Peter Bent Brigham Hospital on Dec. 17, 1920, complaining of headache, vomiting and inability to use the left arm. For eight months there had been weakness in the left arm and leg. For six months, some contraction and flexion of the left hand and extensor contractions of the left foot had been present. For two months, she had had headache and vomiting. One week prior to admission, generalized convulsions occurred for the first time.

Physical Examination.—The positive observations were: (1) left-sided paresis; (2) paresis of the lower extremity, associated with some hypotonia and absence of reflexes; (3) paresis of the left arm, associated with hypertonicity, contractures, flexion of the wrist and increased reflexes; (4) marked intention tremor of the left arm and leg; (5) left pupil smaller than the right; bilateral choked disks of from 4 to 5 diopters; (6) left homonymous hemianopia; (7) past-pointing tests performed very poorly on the left, but fairly well on the right; marked ataxia on the left; (8) suggestion of cracked-pot resonance.

Impression.—The impression was that the condition was a right subcortical or cortical tumor.

First Operation.—Dec. 31, 1920: A cyst in the right temporal region was evacuated and filled with air. The operation was abandoned on account of the patient's rapid pulse.

Second Operation.—Jan. 5, 1921: Transection of the cortex was done with removal of a large amount of gliomatous tissue.

Postoperative Course.—The patient made a good recovery. The choked disks receded, with rather marked secondary atrophy. The left homonymous hemianopia persisted. The intention tremor was markedly decreased. The child was discharged on Jan. 22, 1921.

Subsequent Course.—The patient remained in bed at home for approximately three months. She then began to get about, but was unsteady, walking with a wide base. She went to school, was promoted from grade to grade, and "was able to do everything the other girls did." There was no change in vision. In July, 1924, she began to have attacks of twitching of the left side of face, the left arm and the left leg. These came in short spells of from two to three a day and were not associated with unconsciousness. At the same time she became more irritable, and her memory began to fail. There was progressive weakness of the left arm, left leg and left side of the face.

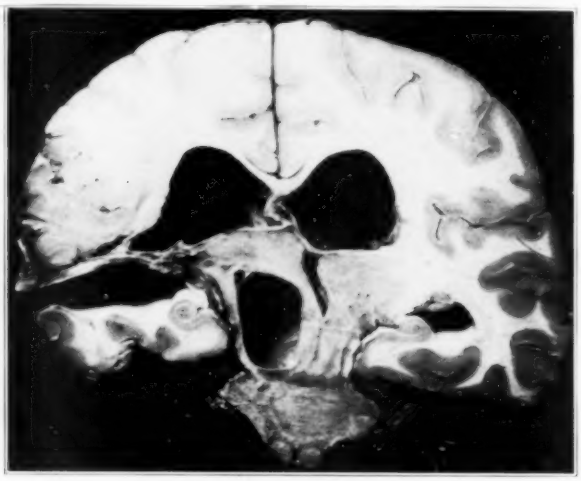

Fig. 4 (case 3).—Large astrocytomatous cyst of the right temporal lobe compressing and destroying a large part of the right basal ganglia. The patient presented rigidity of the left arm, marked intention tremor of the left arm and leg, left hemiparesis and clonic convulsions.

Examination on Readmission.—Jan. 5, 1925: The objective observations were: (1) left homonymous hemianopia; (2) bilateral secondary atrophy; (3) bilateral nystagmus, more marked on looking to the left; (4) hypesthesia of the left side of the face, arm, body and leg; (5) left lower facial weakness; (6) weakness of the left sternocleidomastoid and trapezius; (7) poor memory, euphoria and effusiveness; (8) increased reflexes on the left side; absence of ankle jerks; (9) atrophy of the muscles of the left arm, contracture and atrophy of the left hand and foot.

Impression.—The impression was that the condition was a recurrence of the cystic glioma of right temporosphenoidal area.

Operation.—Jan. 15, 1925: A cyst was evacuated that contained 30 cc. of fluid. Further exploration was not pursued on account of the patient's condition.

Postoperative recovery was excellent, with definite improvement, and the patient was discharged on Feb. 1, 1925.

Subsequent Course.—April 8: The child became semicomatose, and 40 cc. of fluid was evacuated, with relative improvement for a few weeks. She then began to complain of headaches, vomited many times and relapsed again into a semicomatose condition and was readmitted to the hospital on April 26, 1925.

Reexamination.—The decompression area was quite tense; the pulse was very weak. The reflexes were increased on the left. There were paresis and atrophy of the muscles of the left side of the body, which were more marked in the hand and forearm. Hypesthesia was present on the left side. There was bilateral secondary optic atrophy. There was no longer strabismus or facial palsy. The condition of the patient rapidly grew worse, and she died on April 29, 1925.

Necropsy.—There was a large cyst involving the right temporal lobe and basal ganglia. The third ventricle was widely dilated and full of dark cystic fluid. A mural nodule of grayish tumor, about 1.5 cm. in diameter, was present at the base of the cystic cavity.

Diagnosis.—The diagnosis was astrocytoma protoplasmaticum (fig. 4).

CASE 4.—*Global aphasia. Right hemiplegia and hemihypesthesia. Rigidity. Right subtemporal decompression. Rapid course. Death. Autopsy: Glioblastoma multiforme.*

History.—Alberta C., a married woman, aged 54, the mother of three children, was admitted to the Peter Bent Brigham Hospital on April 6, 1923. The family history is without significance. One and one-half years before, the patient's friends began to notice what were considered mental changes. She became somewhat morose, worried and brooded over trifles, was rather idle and sat about a good deal, whereas formerly she had been very industrious. For six months there was dragging and scuffling of the right foot, which had progressed steadily until the time of admission. For five months, she complained of numbness and a peculiar feeling in the right arm and leg. She continued, however, to be up and about the house, walked up and down stairs, and did a small amount of housework. For the past few weeks mastication had been carried out with difficulty. Seven days before admission, she lost the ability to stand and to use the right arm, and was confined to bed. Three days before, she had an attack of vomiting, once before breakfast and twice more during the day. She became more drowsy and was unable to speak except for the words "yes" and "no" in response to questions asked her. She had not complained of headache, but for the past two days had held the hand over the left frontal region, and if asked if she had headache occasionally responded in the affirmative. There had been no complaint of difficulty in vision or hearing. She had had no convulsions or twitchings of the muscles of the face, arm or leg. She had not been incontinent of urine until the day of admission.

Physical Examination.—There was a definite haziness of the disks, with tortuosity of the retinal veins but with no elevation. There was anesthesia of the right cornea and loss of sensation over the area supplied by the right fifth nerve. There was a questionable slight facial weakness on the right. There were increased reflexes of the right arm and leg. A Babinski sign was present on the right, but was questionable on the left. There was loss of sensation over the right leg as compared with the left. The patient was almost completely aphasic, only now and then responding with "yes" or "no" to questions asked.

Impression.—The impression was that the condition was brain tumor of the left parietotemporal region.

Operation.—April 11, 1923: A right osteoplastic exploration was done with negative results. Decompression was performed.

Postoperative Course.—April 13: The condition had been unchanged since the operation. The patient remained uncooperative and completely aphasic. There was a right hemiplegia with right facial weakness as before.

April 18: Five convulsive attacks, of from one to three minutes' duration, occurred during the day with rigidity of the right side of the body and clonic contractions of the masseter and temporal muscles, with the eyes directed to the right.

April 21: The right side (arm and leg) was held absolutely rigid in extension. The left arm and leg were also somewhat stiff. The deep reflexes on the right were all greatly exaggerated. The Babinski sign was positive on right and left.

April 22: The right arm and leg were stiff, but one could not detect any difference between the extensor and flexor groups. There was no response to plantar stimulation. The reflexes were exaggerated on both sides, slightly more so on the right.

April 24: Death occurred.

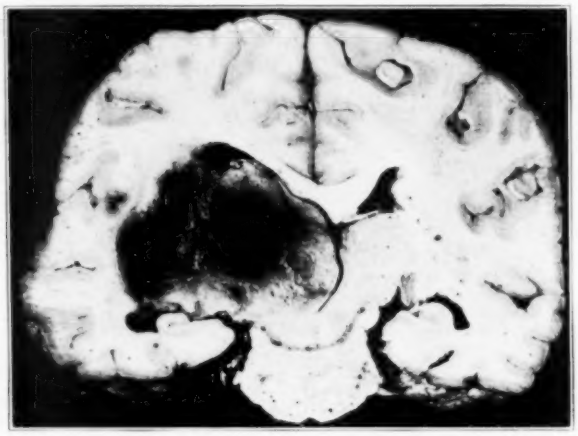

Fig. 5 (case 4).—A coronal section through anterior part of the pons showing a tumor occupying the area of the left optic thalamus. The patient presented a global aphasia, right hemiplegia and hemihypesthesia, and rigidity of the right side of the body.

Autopsy.—A section through the anterior part of the pons showed a fairly well circumscribed tumor mass, about 4 by 5 cm., reddish brown in color, rather firm in consistency, which occupied the area of the left optic thalamus and extended from the corpus callosum above to the upper surface of the substantia nigra below, and out to the cortex.

Diagnosis.—The diagnosis was glioblastoma multiforme (fig. 5).

CASE 5.—*Tremor of the left arm. Left hemiparesis and hemihypesthesia. Ataxia of the left side of body. Right subtemporal decompression. Death. Autopsy: Intratumoral hemorrhage. Glioblastoma multiforme.*

History.—Herbert de F., an architect, aged 29, was admitted to the Peter Bent Brigham Hospital on Dec. 4, 1914. For about five months, he had noticed a decrease in vision and difficulty in reading common print. At the same time weakness of the left side of the body was observed. A spell of vomiting which

occurred at this time and lasted about two weeks was considered as a bilious attack. Following this the patient was able to be about and devote a part of his time to his office, but his gait was staggering and he had some difficulty in speaking. Three weeks before admission to the hospital, he had another attack of nausea very similar to the first one. Since then he had had occipital headache. Diplopia had also been noticed occasionally during the past four months.

Physical Examination.—The objective observations were: (1) nystagmus; (2) weakness of the left side; (3) bilateral choked disks, 5 diopters; (4) pupils very small and reacting sluggishly to light; (5) oculomotor muscle palsies; (6) conjugate deviation of the eyes impossible upward and to the right; (7) slight left lower facial palsy; (8) slight deafness on the left; (9) slight hemihypesthesia on the left; (10) the left foot colder than the right; (11) deep reflexes exaggerated; (12) diadokokinesis poor on the left; (13) ataxia in the left arm and leg; (14) with the arms outstretched, the left sank rapidly; (15) slight coarse tremor of the left arm.

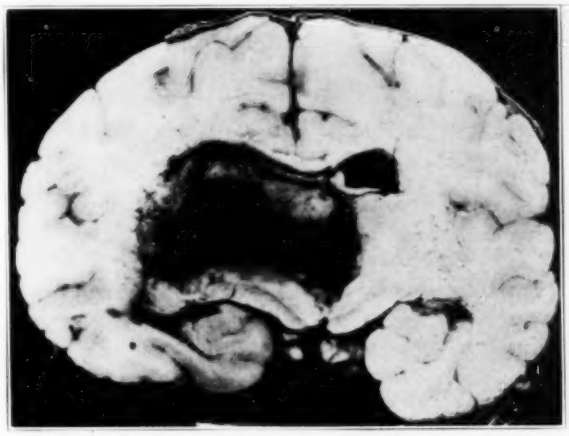

Fig. 6 (case 5).—Large tumor in the region of the right basal ganglia and extending toward the left thalamus. The patient presented tremor of the left arm, left hemiparesis and hemihypesthesia, and ataxia of the left side of the body.

Impression: The impression was that the condition was tumor in the region of the corpora quadrigemina.

Operation.—Dec. 10, 1914: Right subtemporal decompression was performed. Puncture of the lateral ventricles was attempted; no fluid was obtained.

Postoperative Course.—The patient made a good recovery, but his condition remained unchanged. He was drowsy and did not respond well.

December 12: The patient had a severe vomiting spell, during which the pulse rate went up to 140 and respirations became very shallow and irregular. There was a constant coarse twitching of the right arm and leg and a fibrillary twitching of the muscles of the right side of the face and neck. He responded slowly to questions and said he had no pain. Death occurred on December 13.

Autopsy.—There was a very marked pressure cone of the cerebellum. The lateral and third ventricles were dilated. There was nothing in the neighborhood of the oculomotor nerve to account for the paralysis. The coronal section just

anterior to the pons passed through an enormous soft hemorrhagic glioma, which appeared to have invaded the region of the basal ganglia on the right and to have extended over somewhat toward the basal ganglia on the left (fig. 6).

Diagnosis.—The diagnosis was glioblastoma multiforme.

1. *Rigidity as Shown in Group 1.*—It is clear that in these cases one is not dealing with the generalized skeletal hypertonia of striatal disorders. In the latter condition, though the tone may vary from time to time, constituting a state of dystonia, the rigidity is not confined to the limbs as in the cases described, but involves also the face, throat, larynx, trunk etc. Furthermore, a prominent feature of the rigidity of progressive lenticular degeneration is that it does not single out special groups, as flexors or extensors, but affects all groups more or less equally.

In the cases here presented there were special attitudes of the limbs, which are characteristic in that they show a liberation of the mesencephalopontile centers from pyramidal control. These are, in cases 1 and 2, extension-pronation of the arm, flexion of the wrist and retraction of the head laterally and backward, or, as in case 4, complete extension. As Wilson [33] demonstrated, these signs are typical for complete or partial decerebrate rigidity. Indeed, it is well known that parallel with the complete decerebration described by Sherrington, which manifests itself by the fore limbs in extension-pronation, the head in retraction, opisthotonos, and the hind limbs in extension, there also exist limited "fragmentary" forms of decerebration which are more frequent in man, being confined to a whole or to one part of a limb. In incomplete decerebration, therefore, one of these signs may appear alone, being then modified by the fact that an attitude depends not only on the muscles involved directly in the position, but also on those of the neighborhood, the tonic state of which may become preponderant.

It is known that in semidecerebrate animals:

> . . . If instead of both cerebral hemispheres one only is ablated the decerebrate rigidity appears, though not with the same certainty as after double ablation, chiefly on the same side as the hemisphere removed. The monkey, when slung after ablation of one—e. g., the right—hemisphere, exhibits generally the following attitude: The right limbs are extended in the pose described as characteristic for decerebrate rigidity, the tail is strongly incurvated toward the right, that is, its concavity is toward the right and its tip is also toward the right. *The head also is pulled toward the right and retracted. The left forelimb is sometimes distinctly more flexed* than would be expected in the paralyzed condition of the animal; *the left knee likewise.* [Italics are mine.] The contrast between the attitude of the crossed and homonymous sides is very striking (Sherrington [34]).

33. Wilson, S. A. K.: On Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, Brain **43**:220, 1920.

34. Sherrington, C.: Decerebrate Rigidity, and Reflex Coordination of Movements, J. Physiol. **22**:319, 1897.

Flexor rigidity has been noted in decerebrated animals by other workers. Recently, Pollock and Davis [35] observed it in their studies on decerebration by the anemic method. Bazett and Penfield,[36] working on chronic as well as on acute decerebrate preparations of cats, have already proved that an extensor rigidity may alternate with one of flexion. Their opinion was that "it would be more accurate to speak of extensor and flexor rigidity as two types of decerebrate rigidity."

2. Cerebellar Fits.—In his studies on decerebration, Sherrington [34] has further observed that:

> Homonymous extensor rigidity consequent on ablation of one hemisphere is neither so constant of production nor so persistent when it appeared as the rigidity following bilateral ablation. *After coming on it may totally subside and again reappear and so on several times over.* [Italics are mine.] There would seem under these circumstances a struggle between two conflicting influences, as though a tonic influence from the still intact hemisphere at times overcame and at times was overcome by another opposed influence from another center. Some amount of extensor rigidity on the side opposite to the lesion is not uncommon.

This same phenomenon was noted in the cases just described. The tonic fits which Jackson has attributed to the cerebellum, erroneously considering the latter as a center of tone, and which are still wrongly designated as "cerebellar fits" because they are often present in cerebellar lesions and also in cases of subtentorial arachnoiditis, are nothing but a manifestation of partial decerebration. Wilson,[33] in reporting five cases in which this symptom represented one of the characteristics of a syndrome of typical decerebration, had already concluded that "tonic fits are in reality attacks of decerebration."

3. Tremor and Involuntary Movements.—The tremor observed in case 2 is perhaps nothing other than a manifestation secondary to the rigidity. As Jackson has expressed it: "tremor differs from rigidity not fundamentally but in degree." The rhythmic and slow tremor noted here may possibly be just a wavering caused by disbalance of the antagonistic muscles the tone and muscular capacity of which are not equal. But, since in these cases in addition to the tremor bilateral involuntary movements were also present, it would be more plausible to impute these symptoms to a hypothalamic lesion.

In case 3 it is probable that the marked intention tremor was a symptom of cerebellar compression, just as the nystagmus, the hypotonia, the staggering gait, the pastpointing and the adiadokokinesis noted in this case.

35. Pollock, L., and Davis, L.: The Reflex Activities of a Decerebrate Animal, J. Comp. Neurol. **50**:377, 1930.

36. Bazett, H., and Penfield, W.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain **45**:185, 1922.

In cases 1 and 5, choreo-athetoid movements and slight tremor were the only signs pointing to a lesion of the subthalamus.

4. *Conclusions.*—In this group of cases, apparently illustrative of a disease of the basal ganglia, there is a complete lack of any symptoms permitting a localization of a lesion in these structures.

GROUP 2.—This group is composed of tumors of the basal ganglia without any localizing symptoms. The two following cases are illustrative of the whole series of twenty cases.

CASE 6.—*Left hemihypesthesia and pyramidal deficiency. Exploratory craniotomy without disclosing tumor. Rapid postoperative course. Fatality. Autopsy: Atypical glioma.*

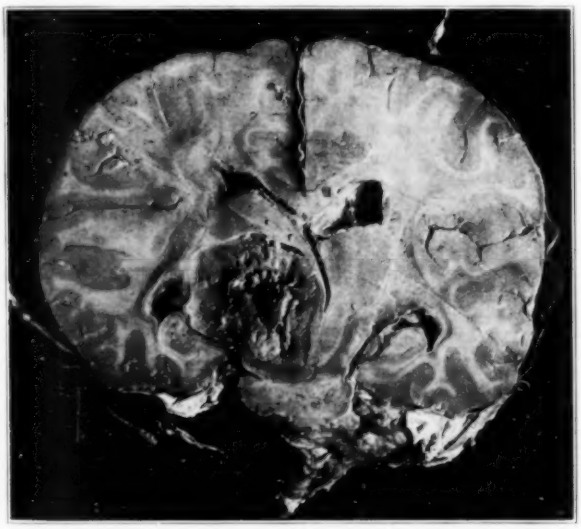

Fig. 7 (case 6).—Encapsulated growth that appears to be directly in the internal capsule and apparently originating in the right basal ganglia. The patient presented a left hemihypesthesia and pyramidal deficiency, but no symptoms of basal ganglia involvement.

History.—Roger S., a schoolboy, aged 10, was admitted to the Peter Bent Brigham Hospital on Dec. 7, 1916. Nine months before, it was noticed that he was wearing off the toe of the left shoe and that he had a slight limp. A photograph taken at that time showed a facial asymmetry similar to that at the time of admission. At the same time it was also observed that the left arm was becoming stiff and weak. Since then, the condition had slowly grown worse. Since the onset, the patient complained of pain at the back of the occiput, and six months before admission to the hospital of pain in the left shoulder and arm, which was of short duration. About four weeks before, following a spinal tap, with the fluid under considerably increased pressure, there were severe suboccipital headache, diplopia, nausea and vomiting for several days. This gradually cleared up. There

was no history of staggering gait or failure of vision aside from the temporary diplopia of four weeks before admission.

Physical Examination.—The positive objective observations were: (1) left-sided weakness, including the arm and leg, and the left seventh, ninth, eleventh and twelfth nerves; (2) relative hemihypesthesia and analgesia on the left; (3) choked disks of 2 diopters; (4) stiffness of the neck; (5) suggestive cracked-pot sound; (6) right pupil irregular and immobile to light, the left sluggish and larger than the right; (7) superficial reflexes diminished on the left; (8) deep reflexes exaggerated on the left; (9) ankle clonus and patellar clonus on the left; (10) Babinski and Oppenheim signs on the left; (11) normal x-ray picture.

Clinical Diagnosis.—The clinical diagnosis was right paracentral, subcortical tumor; tuberculoma?, glioma?.

Operation.—Dec. 19, 1916: Right exploratory craniotomy was performed. An internal hydrocephalus was found. An incision was made in the cortex to the ventricle without disclosing a tumor.

Postoperative Course.—December 20: The patient could not be aroused. The right pupil was markedly dilated. The right knee jerk was absent; supra-orbital pressure alone caused motion of the limbs. There was obviously an increase in intracranial pressure causing stupor. On reelevation of the flap, a small clot was found. The patient's condition at once improved.

December 21: The patient was again stuporous. Examination showed a contracted pupil on the left and increased reflexes. A needle was inserted in the wound, but no fluid was obtained.

December 22 to 27: The condition was slightly improved.

December 29: During the last forty-eight hours, the child again became stuporous. The ventricle was punctured, but no fluid obtained. Death occurred a few hours later.

Autopsy.—A section through the infrapeduncular spaces passed through what appeared to be the center of a fairly definitely encapsulated growth, which appeared to lie directly in the internal capsule, destroying the basal ganglia on the right side (fig. 7).

Diagnosis.—A diagnosis of atypical glioma was made.

CASE 7.—*Aphasia. Right hemihypesthesia and pyramidal deficiency. Exploratory craniotomy without disclosing a tumor. Rapid postoperative course. Death. Autopsy.*

History.—Henrietta G., a woman, aged 54, almost totally aphasic, was admitted to the Peter Bent Brigham Hospital on Feb. 28, 1931. She was, however, still able to cooperate slightly in the examination. The history was obtained from her son. Drowsiness apparently was the first symptom and was noticed about three weeks before, since when it had gradually progressed. At the same time, a marked weakness of the muscles of the face on the right side was observed. About three weeks before, the patient began to use the wrong words; this progressed until she had lost intelligible speech. Although no definite history of headache was obtained, the patient was evidently suffering from frontal headache after admission.

Physical Examination.—The objective observations were: (1) slight bilateral choking of the disks, without measurable elevation; (2) right homonymous hemianopia; (3) slight nystagmus on looking to the left; (4) marked right lower facial weakness and right hemiparesis, particularly of the arm; (5) right hemihypesthesia, more marked in the face than in the leg; (6) right abdominal reflexes absent;

right extensor toe response; deep reflexes more active on the right; (7) patient very drowsy, almost completely aphasic and incontinent. The x-ray pictures were normal.

Impression.—The impression was that the condition was a left temporal tumor.

Operation.—March 7, 1931: A left osteoplastic flap was made with subtemporal decompression. A transection was made of the temporal lobe without finding a tumor.

Postoperative Course.—March 8: Following the operation, the patient became quite unconscious and remained so all night. Suddenly the temperature rose to 105 and 107 F., and she died soon after.

Autopsy.—A section through the infrapeduncular space passed through a tumor located in the left basal ganglia (fig. 8).

Diagnosis.—Glioblastoma multiforme was diagnosed.

Fig. 8 (case 7).—A very large tumor located in the left basal ganglia, which had caused symptoms of aphasia, right hemihypesthesia and pyramidal deficiency without any specific signs of involvement of the basal ganglia.

CONCLUSIONS

Contrary to generally accepted opinion, and also contrary to the conclusions of Mingazzini [37] and others who, on the basis of cases of tumor of the corpus striatum, have claimed to have established or confirmed a definite lenticular syndrome, the twenty-five cases of tumor of the basal ganglia here discussed do not present any specific signs.

Most of the symptoms, which were apparently characteristic of a disorder of this region, are nothing but manifestations of a partial decerebration. Whether the latter is due to a mesencephalic transection

37. Mingazzini, G.: Das Linsenkernsyndrome, klinische und anatomisch-pathologische Beobachtungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:85, 1912.

by the tumor or to an inhibition of the telencephalon by secondary hydrocephalus, one must keep in mind that such a condition may also be met with in basal meningitis, in cerebellar lesions, in pinealomas, in intraventricular hemorrhages and in ruptured abscesses (Bastian,[38] Bruce,[39] Turner,[40] Wilson[33]). Furthermore, similar symptoms have been observed in Dr. Cushing's clinic by me in such cases as a large meningioma of the olfactory groove and an extensive craniopharyngioma in a child.

Since symptoms of decerebration were present in only two of the entire series of cases reported, they must be considered to be rather an exception. The absence of any characteristic symptoms for basal ganglia lesions may explain the fact that in none of the cases reported was a diagnosis made of involvement or destruction of the basal ganglia.

Specific focal signs indicating a condition of the basal ganglia have not been apparent from the study of this series of cases.

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38. Bastian, Charlton: A Case of Apoplexy in a Boy Aged 15: Intraventricular Haemorrhage; Convulsions and Death in Four Hours, Tr. Clin. Soc. London **17**:21, 1884.

39. Bruce, A.; Pirie, J., and Macdonald, W.: Aneurysm of the Anterior Cerebral Artery with Unusual Prolongation of Life After Rupture; Autopsy, Rev. Neurol. & Psychiat. **6**:449, 1908.

40. Turner, C.: A Case of Prolonged Hyperpyrexia in a Child with a Midbrain Tumor, Brit. J. Child. Dis. **13**:261, 1916.

PRIMARY FIBROBLASTOMA OF THE BRAIN*

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PHILADELPHIA

Fibroblastoma that is primary within the brain substance is rare. We know of only three reported instances that have been verified histologically: that of Mallory, reported recently by Bailey,[1] a case of Bailey's and a recent case reported briefly by Tracy Mallory.[2] We have had the opportunity recently to study such a tumor removed at operation, and we report it because of its rarity and because of the interesting and important theoretical questions aroused by the study of the pathologic specimen.

REPORT OF CASE

Vague history of headaches for two years. Sudden onset of symptoms three weeks before entrance with pain and discharge from the right ear and weakness of the left arm and leg. Objectively, left hemiparesis with Babinski sign, a mixed type of aphasia, hypesthesia over the left side of the body, 14 mm. of pressure in the spinal fluid and evidence of right mastoiditis. Diagnosis of brain tumor in the right motor region. Exposure and enucleation of a subcortical growth 1 cm. below cortex; histologically, a fibroblastoma.

History.—L. H., a man, aged 52, admitted to the Graduate Hospital on Sept. 24, 1930, in the service of Dr. J. C. Yaskin, was in a rather stuporous condition and was unable to give an account of himself. The history was therefore obtained from relatives. A brother, who employed the patient in a general store, had observed during the past two or three years that he occasionally complained of headaches of an indefinite nature. For the past one and one-half years or more, he had had difficulty in gaging distance. This became more pronounced in the few months before entrance, when it was noticed that he missed objects for which he reached, that he had difficulty in driving a car, and that he was unable to get into the garage without touching the door. There was no history of convulsions or lapse of consciousness, nor was there any history of vomiting.

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* From the Neurosurgical Laboratory in the University Hospital and the Wards of the Graduate Hospital of the University of Pennsylvania.

* Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

1. Bailey, P.: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**:1359 (April) 1929.

2. Mallory, Tracy B.: Case Records of Dr. Richard C. Cabot, New England J. Med. **203**:174 (July 24) 1930.

The condition became definitely worse on September 5 about three weeks before entrance to the hospital, when, after prolonged exposure to cold in an ice chest, an infection of the upper respiratory tract developed; a few days later there appeared pain in the right ear, followed by a slight discharge from this ear. The patient continued working until about September 10, when it was noticed that he had weakness in the left arm and leg. Within a few days, in addition to the weakness, there developed numbness in the left arm and leg and staggering to the left. A few days later, there developed pronounced somnolence, weakness and later almost complete paralysis of the extremities of the left side. It was noticed also that his speech became indistinct, and his mind was clouded. It is important to note that he was left-handed. In the last few weeks, there was no headache, vomiting or subjective complaints of visual disturbances. The temperature was said to be normal, and examination of the spinal fluid before entrance showed a manometric pressure of 14 mm. of mercury.

Examination.—The patient was well nourished; he was in a lethargic condition. There was a pronounced fetor oris; the pharynx was injected. Examination of the neck and the thoracic and abdominal viscera revealed no distinct abnormalities. Neurologic examination revealed that he was very somnolent; in fact, he fell asleep on the slightest opportunity. His speech was thick; he had difficulty in comprehending questions; he showed, in short, a distinct mixed aphasia with inability to carry out simple commands and inability to name simple objects.

The pupils were contracted; they did not react to light but responded well to distance. There were: weakness of the left lower part of the face, protrusion of the tongue to the left, pronounced weakness of the left arm and leg, with a Babinski sign on this side, and definite hypesthesia over the entire left half of the body. Otherwise, the neurologic examination revealed nothing of importance. There was no evidence of papilledema; because of the mental condition of the patient, studies of the visual fields could not be made.

The spinal fluid was under a pressure of 14 mm. of mercury. It contained 9 cells. The Wassermann reaction of both the blood and the spinal fluid was negative. The right mastoid cells showed the presence of an old suppurative mastoiditis. The temperature, pulse, blood pressure and leukocyte count were all normal.

Course.—After admission to the hospital, the patient became rapidly worse. He became stuporous and incontinent. Despite the history of an acute onset, with earache and roentgen evidence of mastoid disease, a diagnosis of a right pretentorial tumor was made and operation advised.

Operation.—On September 27, Dr. Grant reflected a right frontotemporal bone flap under local anesthesia. On reflection of the dura, there was found an area in about the middle of the motor cortex in which the sulci were flattened and the cortex pale and resistant.

A transcortical incision in this region led down at a depth of about 1 cm. to the surface of a firm but apparently encapsulated tumor. When removed, it measured about 4 cm. in diameter. The tumor was removed in toto, but the patient died seventy-two hours after the operation. Necropsy, which was complete, failed to reveal a tumor anywhere except in the brain.

The Tumor.—Gross Description: The tumor was roughly egg-shaped, about the size of a walnut. It measured 5 cm. long, 2.5 cm. wide and 5 cm. deep. It seemed well defined and was covered by a thin capsule that was apparently intact over the entire tumor. The surface was covered by a shaggy, fibrinous-appearing exudate. The tumor was slightly lobulated and was extremely firm and resistant to pressure. On section, it was found to consist of a firm, hard portion and a degenerated part. The firm part of the tumor occupied most of the mass. It was

hard, white and fibrous-appearing, and on its cut surface fibrous bands could be seen running in many directions. Large vessels penetrated the tumor here and there.

Microscopic Description: There was a thin capsule around the tumor, but this consisted of only a few strands of fibrous tissue, hardly enough to make a respectable capsule.

The tumor cells ran in streamlets and bands, interdigitating and intertwining like a braid. Some were cut along their longitudinal axes and others at various angles. Even on a cursory glance, the fibrous nature of the tumor was apparent. The cells were loosely packed in some places and in others were crowded together. In some regions there was a definite myxomatous appearance to the tumor. Areas of degeneration were present, sometimes attaining a large size. Blood vessels were numerous in the tumor everywhere. Around the edge of the tumor were typical glia cells, often swollen and hypertrophied and sometimes containing several nuclei. The neuroglia cells were found only on the edge of the tumor, never within its depths.

In addition to the intertwining streams of cells already mentioned, there were areas within the tumor that we have chosen to call centers of growth. Here the cells had a different appearance, were in close relation to the vessels and showed definite evidence of proliferation. In these areas the relation of the cells to the vessels was particularly intimate.

The type cell possessed an oval or round nucleus with a well defined membrane, scattered fine chromatin particles, sometimes a good nucleolus and usually a bipolar aspect to the cytoplasm, which streamed away from both ends of the cell. Such cells were present in the streams already mentioned. In the centers of growth, however, could be seen cells with similar nuclei but with round, polygonal or irregularly shaped cytoplasm. These cells were related to the bipolar elements; this aspect of the matter will be discussed later. Mitoses were frequently encountered among the cells of the tumor.

A rich intercellular substance was found among the tumor cells. It consisted in part of collagen, which was present chiefly around the blood vessels but penetrated for short distances into the tumor among the cells. Reticulin was present, but not in great abundance. The bulk of the intercellular substance was made up of fibrous cells and fibrils which were apparently fibroglia. These fibrils did not stain clearly with the phosphotungstic stain of Mallory, but were seen clearly and in large amounts in silver impregnations of the tumor. They were found in the cells and chiefly in the intercellular tissue. They consisted of long or short, firm, hard fibrils which ran in straight or slightly curving lines. They were particularly abundant in the cells cut along their longitudinal axes. No elastin could be demonstrated.

Of particular interest was the relation of the tumor cells to the vessels. In the so-called centers of growth and elsewhere there could be seen tumor cells grouped around the vessels in a very intimate relation. This arrangement gave to the tumor in these areas a decidedly peritheliomatous appearance. Around the vessels, tumor cells could be seen lying directly on the walls of the venules, capillary vessels and arterioles. They appeared to be an integral part of the vessel in this relationship. Always they appeared to be closely adherent to the outer aspect of the vessel wall, without really giving a lucid idea of how they were genetically related to the vessel. Often, around the vessels one could see cells that showed various stages of development from the more or less embryonic-appearing cell closely adherent to the vessel wall to the bipolar cell that lay not far distant from the vessel.

In the vessels and in the centers of growth the cells differed in type from those of the tumor elsewhere. The cytoplasm was round, ovoid, polygonal or irregularly abundant. One could follow the progress of these immature cells, however, from the vessels to the older tissue immediately around them. Their less mature appearance and their cytoplasmic shape changed from the oval or polygonal cells already alluded to to the bipolar cells that made up the bulk of the tumor.

Specific impregnations failed to reveal the presence of immature glial elements. There were neuroglia cells on the edge of the tumor, but these are present in the glial response to any slowly growing tumor in the brain. No connection could be traced between the tumor cells and the neuroglia cells on the edge of the tumor. A macrophage stain of del Rio Hortega showed many fibroblastic macrophages in the tumor, many of them appearing like microglia cells and many of them, especially in the degenerated areas, appearing like gitter cells. The similarity of these cells to microglia has been mentioned previously by del Rio Hortega [3] and by de Asua.[4]

REPORTS OF PRIMARY FIBROBLASTOMA OF THE BRAIN

Bailey [1] reported a case of fibroblastoma of the brain which was found by Mallory. This was in a woman, aged 42, whose illness had begun three months before admission to the hospital, with unconsciousness, followed by severe frontal headaches and later by twitching of the left leg. She died without an operation having been performed. Necropsy revealed a tumor in the right temporal lobe, measuring 3.4 cm. long, 5.5 cm. in lateral diameter and 4.8 cm. long in vertical diameter. The tumor was semi-opaque and somewhat cartilaginous in the outer portion and opaque, soft, friable and grayish yellow in the central portion. Apparently the tumor was superficial in one portion, because it was described as being adherent to the dura. Inferiorly, it was bounded by the dura, superiorly by the brain tissue over the rolandic area and "internally by the cortical tissue, partially occupying the island of Reil and adjacent to the claustrum." Microscopically, "the tumor was seen to be composed of spindle cells with elongated nuclei having a heavy nuclear membrane, finely granular chromatin, and prominent nucleoli. Mitotic figures were numerous. Between the cells were numerous reticulin and collagenic fibrils but no elastin. Many fibroglia fibrils were easily demonstrated. The microscopic picture was that of a typical fibroblastoma."

Bailey's second case was that of a youth, aged 19, who had been well until about three months before admission to the hospital, when he noticed failing vision. This was followed by vomiting and headache. Examination showed bilateral choked disk of from 5 to 6 diopters, a left homonymous hemianopia, nystagmus, especially to the

3. del Rio Hortega, P.: Concepts histologique, morphologique, physiologique et physio-pathologique de la microglie, Rev. neurol. **37**:956 (June) 1930.

4. de Asua, Jimenez: Die Mikroglia (Hortegazellen) und das reticuloendotheliale System, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:354, 1927.

left, and defective vision in the right eye from cloudy media. A decompression was done, but a left hemiparesis developed one month later, with complete loss of power later in the left arm. The patient had convulsive attacks localized in the left foot and saw yellow lights before his eyes. He was again operated on, and on incision of the brain "on the inner wall of the ventricle could be seen a reddish discoloration indicating an underlying tumor. The tumor was soft, and a large amount was removed by suction." The patient made a good recovery. Microscopically, the tumor "had the typical structure of a fibroblastoma or fibrosarcoma." It was composed of streams of spindle-shaped cells running in various directions. The cells had delicate cytoplasm and oval or elongated nuclei. "The nuclear membrane was heavy; the chromatin was dustlike so that the nuclei had a vesicular appearance, and the nucleoli were prominent. Mitotic figures were numerous. Delicate reticulin fibrils were found between the cells in the more cellular parts of the tumor. Collagen was abundant in the degenerated portions, and delicate fibroglia were present in various parts of the tumor. No elastin was found."

The most recent report is that of Mallory.[2] This concerned a man, aged 38, who first complained of headache and dizziness about three weeks before entrance to the hospital. The headache was frontal but occasionally radiated over the brow to the right. A few days after the onset of the symptoms he vomited. Things had gone black before his eyes about two weeks before entrance, and since the onset of the trouble he had noticed increasing weakness. There were many other symptoms extending over a year and five months referable to the abdomen and chest. Examination revealed bilateral papilledema, left facial weakness, deviation of the palate to the right and diminished knee jerks. The patient was markedly slow mentally and dropped asleep if his attention was not held. He died one month after entrance to the hospital. Necropsy revealed a nodule of tumor, 5 cm. in diameter, in the right frontal lobe. It was of unusual firmness and whiteness. Both suprarenal glands were completely replaced by huge tumors that were almost wholly necrotic and filled with fluid. Microscopic examination revealed two independent primary malignant tumors. "The tumor in the brain was a well-differentiated rather slowly growing, perfectly typical fibrosarcoma." The tumors of the suprarenal glands, tail of the pancreas and heart were similar to each other, but totally different from the brain lesion. The pancreas showed evidence of a primary carcinoma of this organ.

With our case, there are four reported instances of primary fibroblastoma or fibrosarcoma in the brain. Three of the cases were in men and one in a woman. The age incidence is not particularly significant: it was 19, 38, 42 and 52 in the four cases recorded. The most inter-

esting feature of the cases lies in the suddenness of onset and the rapidity of development of the symptoms. In all the recorded cases the symptoms developed suddenly, without premonitory difficulties. In Bailey's first case the onset, three months before entrance, was with unconsciousness. In his second case, the onset was with failing vision about three months before entrance to the hospital. In Mallory's case the first signs were headache and dizziness three weeks before the patient came under observation. The history in our case indicated some evidence of difficulty about two or three years before the patient came under observation. At that time he had vague headaches and some difficulty in gaging distance, first noticed about one and one-half years before he consulted a physician. The main trouble developed only three weeks before entrance to the hospital; following this he developed the localizing signs that made a diagnosis possible.

After symptoms first appear, their development is rapid in this type of tumor. In two cases they developed during the course of three months, while in Mallory's case and also in ours they evolved rapidly during the course of three weeks. In Mallory's case there had been other symptoms for a year and five months, but those referable to the cerebrum developed during the course of three weeks.

Death has occurred in three of the reported cases. In Bailey's first case death occurred in three months without operation. In Mallory's case death occurred from carcinoma of the abdominal organs, while our patient died shortly after operation. The patient in Bailey's second case, operated on by Cushing, was alive at the time of this report.

Three of the four cases have been entirely subcortical, and a transcortical incision has been necessary to expose the tumor. In the first case reported by Bailey, a portion of the tumor was in contact with the dura, in addition to a larger portion that lay within the brain. All the tumors have appeared to be typical fibroblastomas or fibrosarcomas.

Reference should be made to reports of primary sarcoma of the brain by Fried [5] and Cassirer and Lewy.[6] These are not concerned with the type of fibrosarcoma that we are reporting and will not be referred to in detail.

THE NATURE OF THE TUMOR

The typical arrangement of the cells in one case, with their characteristic morphology and the presence of fibroglia fibrils, made the diagnosis of fibroblastoma reasonable, and we have so designated this tumor. Among the other possible diagnoses was that of marked

5. Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **15**:205 (Feb.) 1926.

6. Cassirer, R., and Lewy, F. H.: Zwei Fälle von flachen Hirntumoren, Ztschr. f. d. ges. Neurol. u. Psychiat. **61**:119, 1920.

fibrosis in a glioma that has undergone extensive degeneration. The extensiveness and regularity of the process and the lack of gliomatous structure ruled out this possibility. We are well aware that a glioma that is undergoing repair may show evidences of extensive fibrosis, but we were unable to prove that this was the process at work in our tumor. In addition, the new growth was encapsulated and confined to the structure seen in figure 1, and was not, therefore, an infiltrating growth. No evidence of the presence of a gliomatous tumor was found. Furthermore, the extreme regularity with which the cells of the new growth were deposited is wholly unlike any process of organization within a tumor that we have seen.

The definite tendency on the part of the tumor cells to arrange themselves around the vessels gave to the tumor the appearance in these areas of a perithelioma. The general structure of the tumor,

Fig. 1.—The tumor, which was entirely subcortical, is well encapsulated and sharply defined.

however, was not that of a typical perithelioma. Only in scattered areas was the relationship to the vessels marked, and these we have looked on as centers of growth of the tumor cells. Transitions from the immature cells surrounding the vessels to the spindle-shaped cells constituting the greater part of the tumor were readily traceable.

The only evidence of glia cells was found at the edge of the tumor. None was seen elsewhere. This was apparently a gliosis in response to the advance of the tumor. We were unable to trace any connection between these glia cells and the bipolar cells that made up the tumor. Certainly, no evidence was found for looking on the latter as spongioblasts, either morphologically or on the basis of special impregnations. Moreover, no glia cells, embryologic or adult, were found anywhere else in the tumor, and we therefore discarded the possibility that the tumor was of glial origin.

The fibroblastoma may have taken origin from the pia, the vascular adventitia or the perithelium of the blood vessels. There is no bona

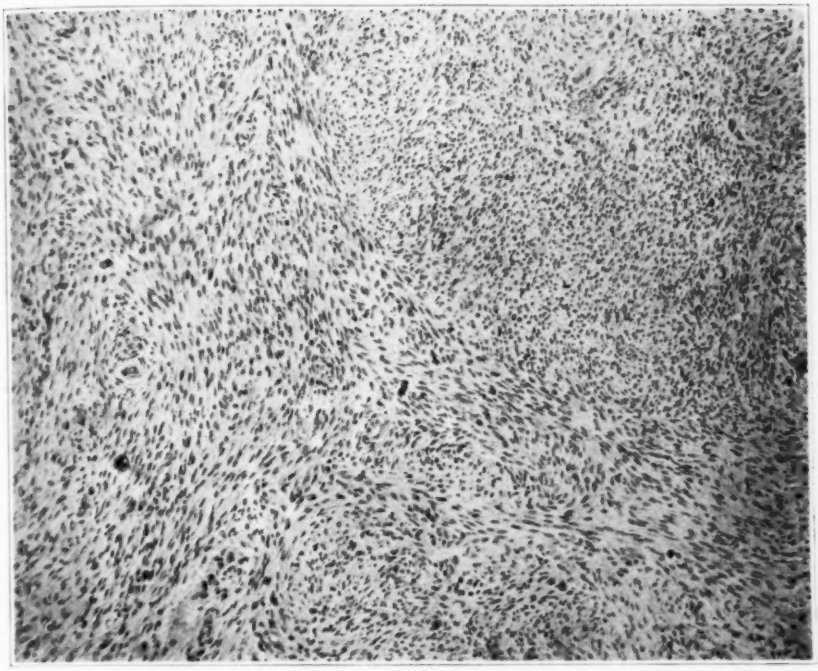

Fig. 2.—The structure of the tumor is well illustrated in this photograph. The cells, arranged in bundles or streams, run in many directions. The fibroblastic nature of the tumor is clearly seen. Hematoxylin and eosin stain.

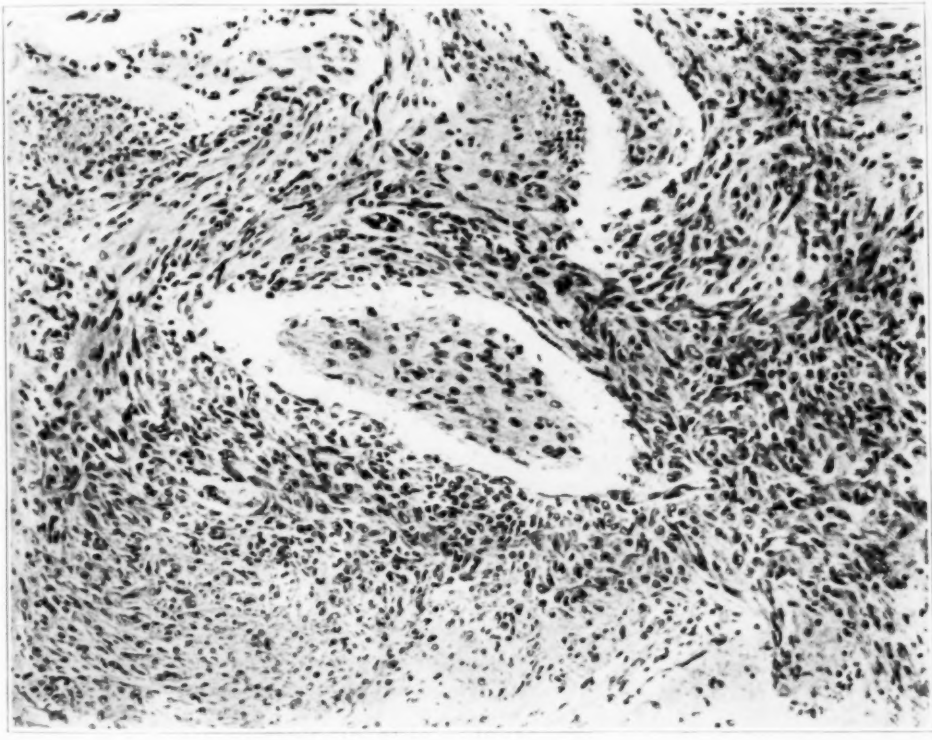

Fig. 3.—"Centers of growth" in the tumor, showing the tumor cells in close relation to the vessels in these centers. Hematoxylin and eosin stain.

fide evidence that there is such a membrane as the perithelium. Maximow [7] stated that the adventitia capillaris, or perithelium, of the older histologists was probably composed of a number of different elements, such as fibroblasts, resting wandering cells, mast cells and plasma cells. He advocated the abandonment of this term because of its indefiniteness. He described, nevertheless, certain branched elements that surround the capillaries. Their cell bodies are stretched along the vessel and send out branches that encircle the tube with a comblike arrange-

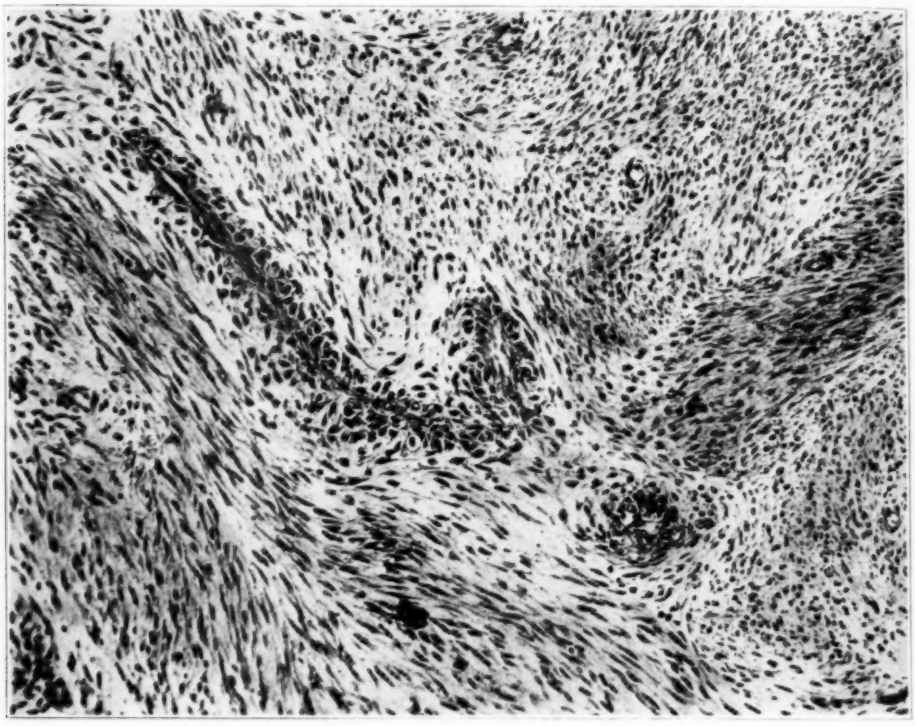

Fig. 4.—In this area the relation of the cells to the vessels is seen. Transitions from the cells close to the vessels and the spindle cells of the tumor are visible even under low power magnification. Hematoxylin and eosin stain.

ment. These cells are usually called pericytes, but their morphologic nature, origin and function are unknown; Maximow apparently considered them histiocytes. While he therefore denied the existence of a perithelium, he admitted the presence of pericytes, which may be cells of a varied character. MacCallum [8] stated unequivocally: "I

7. Maximow, A., and Bloom, W.: Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930, pp. 33 and 85.

8. MacCallum, W. G.: A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 1004.

have searched in vain for perithelium, or even for any clear description of it, and do not believe such cells exist." In a recent review, Benninghoff [9] was unable to give a clear description of perithelium, but he, like Maximow, accepted the existence of pericytes. Whether there exists an adventitial membrane, which is called perithelium, is therefore impossible to state with any degree of certainty, and we cannot say whether our tumor is of perithelial origin. There can be little doubt, however, that around the many vessels in our tumor were tumor cells that were arranged in intimate relation to the vessels. They

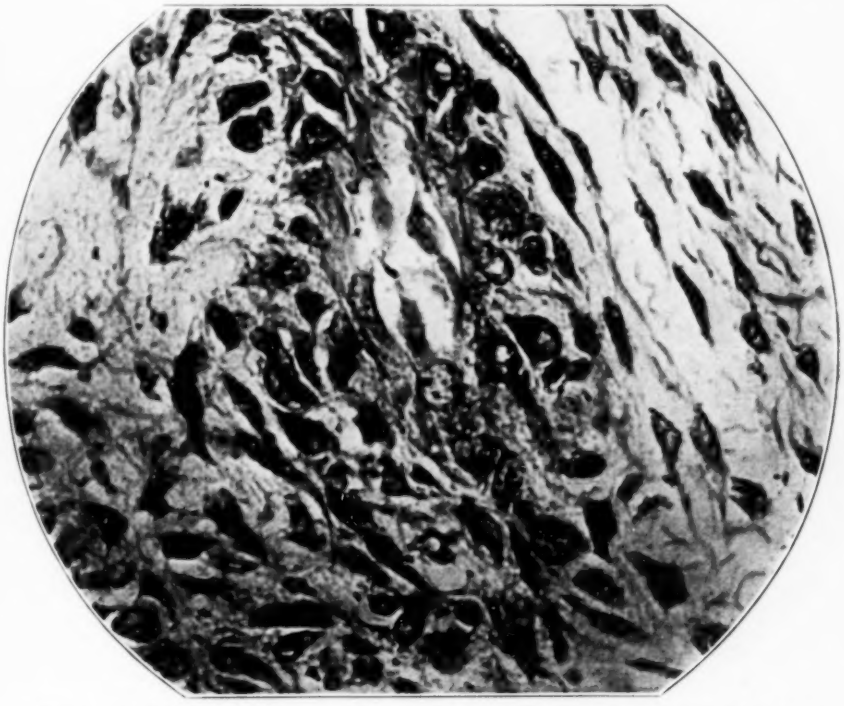

Fig. 5.—A high power photomicrograph of a vessel to show the transition from the immature tumor cells close to the vessel to the spindle cells that constitute most of the tumor. Hematoxylin and eosin stain.

seemed to be part and parcel of the vessel wall. Often the vessels they surrounded consisted only of a single layer of endothelial cells, on the outer side of which were clusters of tumor cells that could be traced in their development to the spindle-shaped element that con-

9. Benninghoff, A.: Handbuch des microskopischen Anatomie der Menschen, Berlin, Julius Springer, 1930, vol. 6. The subject of the existence of a perithelium is complicated. The data for the existence of pericytes can be found in Benninghoff's article.

stituted the bulk of the tumor. Possibly these cells arose from fibroblastic pericytes, or from the connective tissue cells within the pial sheath surrounding the cerebral blood vessels. Their cell of origin was a fibroblastic cell derived either from the sources already mentioned or from cells that were capable of differentiating into mature fibroblasts. The structure of by far the largest portion of the tumor is that of a fibroblastoma, and the cells around the blood vessels, from which we think we were able to trace these adult fibroblastic elements, are either immature fibroblasts or mesodermal elements that are capable

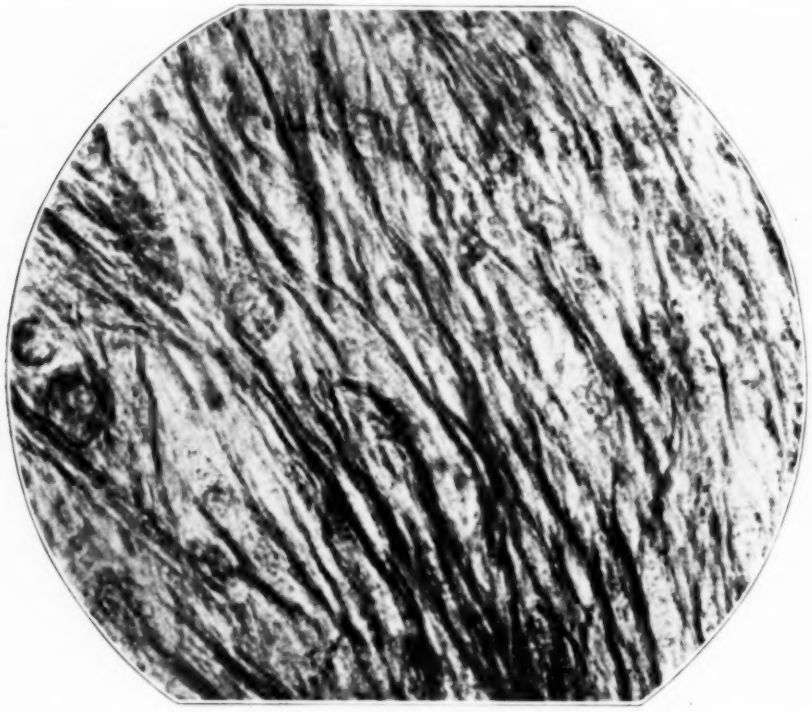

Fig. 6.—Numerous fibroglia fibrils in the tumor. Silver carbonate method of del Rio Hortega.

of differentiating into fibroblastic cells. For reasons already given, we do not believe that our tumor is one of the perithelioma group, largely because its morphologic characteristics do not conform to those of this group of tumors. While we have emphasized the relation of the tumor cells to the blood vessels, we have done so merely to call attention to a possible source of origin of the tumor. The peritheliomatous arrangement was found only scattered around blood vessels, but the major part of the tumor was composed of spindle-shaped elements arranged as described and illustrated.

We are unable to state definitely, therefore, whether our tumor is derived from the fibroblastic pericytes or the pial membrane surrounding the cerebral blood vessels. It is conceivable that either of these elements may have assumed neoplastic properties during the course of development. We can state with certainty, however, that the tumor is derived from mesodermal elements, either fibroblasts or cells that are capable of differentiating into fibroblasts.

ABSTRACT OF DISCUSSION

DR. WILDER G. PENFIELD, Montreal: A very interesting case has been presented. It stands to reason that fibroblastomas may develop from any area of the meninges, whether they be the leptomeninges or the pachymeninges. This is not the place to discuss whether this tumor should be called a hemangioblastoma or a fibroblastoma. It is obviously more rapidly growing than the ordinary meningeal fibroblastoma, and there are also many differences from this tumor in its histologic structure. We know that the ordinary meningeal fibroblastoma — I use that term to mean the type of tumor that has ordinarily been called dural endothelioma — sometimes arises from the leptomeninges not connected with the dura, as pointed out by Elsberg, and that it also arises from the dura not connected with the leptomeninges.

Von Recklinghausen's disease sometimes brings out a neoplastic change in various tissues. These neoplasms are of the type to which these particular tissues are apt to give rise. We see, therefore, in von Recklinghausen's disease ordinary meningeal fibroblastomas occurring in a number of places. A typical meningeal fibroblastoma has been described in the ventricle arising from the choroid plexus. One would expect to find occasionally a true meningeal fibroblastoma within the brain. In general, it is interesting from the point of view of the origin of the meninges and the nature of the meninges that the various types of tumor that arise from it belong to the fibroblastic or sarcomatous type of growth and do not resemble neoplasms derived from ectodermal tissues.

It is difficult to be sure whether the neoplasms reported arose from meningeal or cerebral blood vessels or from the leptomeninges themselves. From the histologic structure one would assume that the origin is not in the meninges. It seems well worth while to put on record all of the tumors of this type that one may encounter arising within the brain.

DR. CHARLES S. KUBIK, Boston: I should like to add a case that appears to be one of primary fibroblastoma of the brain. Although others tumors were found in the body at autopsy, I believe it is quite evident that the tumors are different. The material has been seen by Dr. Frank Mallory, and I had hoped that he would speak about it in his discussion of the paper. He also believes that the tumor of the brain is a primary growth.

The patient was a man, aged 38, who was studied at the Massachusetts General Hospital in Dr. Ayer's service. He had had symptoms of increased intracranial pressure for a month before his death.

DR. BERNARD J. ALPERS, Philadelphia: I was acquainted with the case reported in Dr. Ayer's service. I have reported it in my paper. I am sorry that Dr. Mallory could not be here. I sent him sections of the tumor in our case. He reported the first instance of this sort, and he told me that ours was exactly similar to the type of tumor that he had reported and the second one he had ever seen.

THE RÔLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PRODUCTION OF PAIN IN THE HEAD*

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AND
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The rôle of the sympathetic nervous system in the production of pain has been under investigation since Hilton,[1] in 1863, stated that cutaneous pain was found "occurring on the surface of the body in association with derangements of internal and often remotely situated viscera."

In recent years the investigations have been stimulated by the observations that at times section of the posterior spinal roots and of the fifth cranial nerve fails to produce complete analgesia or to relieve pain, and that section of parts of the sympathetic nervous system does relieve certain pain. The failure to relieve pain by section of the posterior spinal roots and the failure to produce complete analgesia in the deafferented areas led to the proposal by Leonard Kidd that pain could be conducted antidromically over the anterior roots (Lehmann,[2] Foerster,[3] Shawe[4] and Wartenberg[5]). In a former communication we described a series of experiments that resulted in evidence that opposed this conception.

Foerster, Altenburger and Kroll[6] reported observations on man in which pain was produced by suitable stimuli in areas to which the somatic afferent supply had been severed. They believed that the only

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1. Hilton, J.: Lectures on Rest and Pain, ed. 1, London, Bell & Daldy, 1863, pp. 64 and 74; quoted by Hurst, A. F.: The Goulstonian Lectures on the Sensibility of the Alimentary Canal, London, H. Frowde, 1911, pp. 45 and 74.

2. Lehmann, W.: Ueber die sensiblen Fasern der vorderen Wurzeln, Klin. Wchnschr. **3**:1895, 1924.

3. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927.

4. Shawe, R. C.: The Gastric Crises of Tabes Dorsalis and Their Surgical Treatment, Brit. J. Surg. **9**:450, 1922.

5. Wartenberg, R.: Klinische Studien zur Frage der Geltung des Bell-Magendieschen Gesetzes, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:518, 1928.

6. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystem zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:140, 1929.

possible intact afferent pathway consisted of periarterial plexuses of nerve fibers that ended in the sympathetic ganglionic chain. From these observations they believed that sensory impulses may travel along periarterial plexuses to the sympathetic ganglionic chain and from there enter the spinal cord.

The failure of section of the posterior root of the fifth nerve to relieve certain so-called atypical facial neuralgias likewise has called attention to the possible rôle played by the sympathetic nervous system in the production of pain. Therefore, attempts have been made to relieve such pain by injection into the sphenopalatine ganglion (Sluder [7]) or by excision of Meckel's ganglion (Cushing [8] and Frazier [9]), and by section of the various branches of the superior cervical sympathetic ganglion (Frazier). It has led to the assumption that the sympathetic nervous system plays a rôle in the etiology of some cases of atypical neuralgia.

Special emphasis on the importance of this rôle has been made by the reports of the relief of other types of pain by various surgical operations on the sympathetic nervous system. The pain of angina pectoris has been relieved by the removal of the middle, inferior cervical and first thoracic ganglion of the left sympathetic chain by Jonnesco.[10] Successful results have been reported from essentially similar operations by Brüning [11] and others. Coffey and Brown [12] have obtained somewhat similar results by sectioning the sympathetic trunk and the superior cardiac nerve below the superior cervical ganglion or by excising this ganglion. More extensive operations seem indicated by more recent studies (Braeucker [13] and Jonnesco and Enachescu [14]). The literature

7. Sluder, G.: Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1918.

8. Cushing, H.: The Major Trigeminal Neuralgias and Their Surgical Treatment Based on Experiences with 332 Gasserian Operations: I. The Varieties of Facial Neuralgia, Am. J. M. Sc. **160**:157, 1920.

9. Frazier, C. H.: Atypical Neuralgia: Unsuccessful Attempts to Relieve Patients by Operations on the Cervical Sympathetic System, Arch. Neurol. & Psychiat. **19**:650 (April) 1928.

10. Jonnesco, T.: Traitement chirurgical de l'angine de pectrine par la résection du sympathique cervico-thoracique, Presse méd. **29**:193, 1921.

11. Brüning, F.: Die operative Behandlung der Angina pectoris durch Extirpation des Halsbrustsympathicus und Bemerkungen über die operative Behandlung der abnormen Blutdrucksteigerung, Klin. Wchnschr. **2**:777, 1923.

12. Coffey, W. B., and Brown, P. K.: The Surgical Treatment of Angina Pectoris, Arch. Int. Med. **31**:200 (Feb.) 1923.

13. Braeucker, W.: Das Brustteil des vegetativen Nervensystems und seine klinisch-chirurgische Bedeutung, Beitr. z. klin. d. Tuberk. **66**:1, 1927.

14. Jonnesco, D., and Enachescu, M.: Nerfs cardiaques naissant de la chaine thoracique du sympathique, au-dessous du ganglion stellaire: Les nerfs cardiaques thoraciques chez quelques mammifères, Compt. rend. Soc. de biol. **47**:977, 1927.

on these operative procedures is already very extensive and need not be referred to further.

On the basis of the work of Mandl [15] on paravertebral injections, attempts have been made to block the rami communicantes by such a method (Swetlow [16] and White [17]). Abdominal pains have likewise been relieved by von Gaza,[18] Scrimger [19] and Archibald [20] by section of the abdominal sympathetic nerves. The sacral portion of the sympathetic trunk has been resected for the relief of pain in inoperable carcinoma of the uterus. The relief of pain from causalgia, painful stumps and other conditions by periarterial sympathectomy has been widely reported by a large number of observers following the work of Leriche.[21]

Although pain may be produced by stimulation of parts of the sympathetic nervous system or relieved by severance of suitable parts of the sympathetic nervous system, there is no agreement as to the manner in which this pain is produced. Painful impulses may be conducted along the sympathetic nerve fibers, or the visceromotor or other reflex activities may produce conditions which in turn are responsible for conscious pain. On the other hand, both mechanisms may be present.

A number of theories exist for the explanation of the sensation evoked by visceral stimulation. Lennander's [22] idea that all visceral pain was mediated through the parietal peritoneum was disproved by Neumann.[23] Ross [24] stated that either there may be true visceral pain

15. Mandl, F.: Die Wirkung der paravertebralen Injektion bei Angina pectoris, Arch. f. klin. Chir. **136**:495, 1925.

16. Swetlow, G. I.: Paravertebral Block in Cardiac Pain, Am. Heart J. **1**:393, 1926.

17. White, J. C., and White, P. D.: Angina Pectoris; Treatment with Paravertebral Alcohol Injections, J. A. M. A. **90**:1099 (April 7) 1928.

18. von Gaza, W.: Ueber paravertebrale Neurektomie am Grenzstrange und paravertebrale Injektionstherapie: Ein Beitrag sur Behandlung neurotischdysfunctioneller Krankheitzustände bauchinnere Organe, Klin. Wchnschr. **2**:525, 1924.

19. Scrimger, F. A. C.: On the Possibility of Relieving Abdominal Pain by Section of Sympathetic Rami Communicantes, Canad. M. A. J. **21**:184, 1929.

20. Archibald, E.: Effect of Sympathectomy upon the Pain of Organic Disease of Arteries of the Lower Limbs and for Obscure Abdominal Pain, Ann. Surg. **88**: 499, 1928.

21. Leriche, R.: Some Researches on the Periarterial Sympathetic, Ann. Surg. **74**:385, 1921.

22. Lennander, K. G.: Ueber die Sensibilität der Bauchhöhle und über lokale und allgemeine Anästhesie bei Bruch- und Bauchoperationen, Centralbl. f. Chir. **28**: 209, 1901.

23. Neumann, A.: Zur Frage der Sensibilität der innern Organe, Zentralbl. f. Physiol. **24**:1213, 1910-1911.

24. Ross, J.: On the Segmental Distribution of Sensory Disorders, Brain **10**: 333, 1888.

alone or it may occur in association with pain in the skin, muscles and connective tissue innervated by the same spinal segments. Lange [25] thought that all pain in visceral disease was of purely reflex origin. He traced the impulses through the afferent fibers of the vegetative nervous system to the spinal cord, where he believed that radiation occurred along the sensory tracts to the abdominal wall. Spiegel [26] stated that the impulses pass to the posterior horns of the spinal cord and are there diffused to the roots of the corresponding somatic nerves. Mackenzie,[27] Ross [24] and Head [28] believed that in visceral disease a form of irritation is produced in the spinal cord, and that sensory impulses from other parts passing into this segment are so exaggerated as to be painful. It is unnecessary to expound the various ideas further for the purpose of this communication. It is sufficient to point out some of the differences of opinion.

Pain has been produced by faradic stimulation of the superior cervical sympathetic ganglion in man by Frazier and Russell,[29] Peet [30] and Foerster.[3] The head is a particularly suitable part of the body for the investigation of the rôle of the sympathetic nervous system in the production of pain, because it is possible to cut all of the posterior roots possibly connected with the cervical sympathetic chain without producing an analgesia of the skin overlying the parts from which painful sensation may occur. As it is conceivable that the superior cervical ganglion and its immediate environs are supplied with sensation by nervi nervorum, it is necessary to deafferent this area when one wishes to study the results of faradic stimulation of the ganglion. The head is also suitable because of the general agreement as to the composition of the cervical sympathetic chain. Langley [31] has shown that section of the cervical sympathetic trunk central to the superior cervical ganglion

25. Lange, C.: Nogle bemärkninger am neuralgier og deres behandling, Hospitalstid. **2**:641, 1875.

26. Spiegel, E.: Ueber das Wesen des Bauchschmerzes und seiner Begleiterscheinungen, Wien. med. Wchnschr. **77**:379, 1927.

27. Mackenzie, J.: Symptoms and Their Interpretation, London, Shaw & Sons, 1920.

28. Head, H.: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease, Brain **16**:1, 1893; **17**:339, 1894; **19**:153, 1896.

29. Frazier, C. H., and Russell, E. C.: Neuralgia of the Face: An Analysis of 754 Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, Arch. Neurol. & Psychiat. **11**:557 (May) 1924.

30. Peet, M. M.: Postherpetic Trigeminal Neuralgia: Persistence of Pain After Section of the Sensory Root of the Gasserian Ganglion, J. A. M. A. **92**:1503 (May 4) 1929.

31. Langley, J. N.: Observations on the Medullated Fibers of the Sympathetic System and Chiefly on Those of the Grey Rami Communicantes, J. Physiol. **20**:55, 1896.

caused complete degeneration of the fibers up to the ganglion. Peripheral to the ganglion no evidence of degeneration was found. This evidence of an absence of afferent fibers in the cervical sympathetic trunk was strengthened by the work of Ranson and Billingsley.[32] These investigators have shown rather conclusively that there are no descending fibers in the superior cervical sympathetic trunk, and have pointed out that there are no preganglionic fibers in the branches of the superior sympathetic ganglion. They also showed that the postganglionic fibers that arise from the superior cervical sympathetic ganglion are distributed to the trigeminal, glossopharyngeal, vagus and hypoglossal nerves. This work has been corroborated recently by Cleveland.[33] He has shown by degeneration experiments that no myelinated fibers remain in the central end of the sympathetic trunk that has been sectioned between the superior cervical and stellate ganglia. Neither has he been able to find any evidences of degeneration in the fibers of the carotid nerve plexus or in any of the other branches of the superior cervical ganglion. On an anatomic basis, therefore, the sympathetic supply to the structures of the face and head must be considered as consisting of purely efferent fibers. A diagrammatic representation of the superior cervical sympathetic ganglion is shown in figure 1.

EXPERIMENTAL STUDIES

In an effort to determine the rôle of the sympathetic fibers in the production of pain in the face, we carried out the following group of experiments on a series of thirty-five cats.

Stimulation of the Cervical Sympathetic Trunk Does Not Produce Pain.—Though there is anatomic evidence to show conclusively that there are no afferent fibers in the cervical sympathetic trunk, we stimulated this structure with a faradic current. We found that the only effects produced were a dilatation of the pupil on the same side and a movement of the nictitating membrane. There was no evidence whatever of the production of pain as shown by struggling, crying out or movement of the tail of the animal. All of these and the succeeding experiments were carried out under very light ether anesthesia. At all times the corneal, sneeze, pinna and spinal reflexes were present and easily elicited. The same negative evidence of the production of pain was obtained by stimulation of the central or distal ends of the divided sympathetic trunk. This work has also been corroborated by Cleveland [33] (fig. 2).

32. Ranson, S. W., and Billingsley, P. W.: Branches of the Ganglion Cervicale Superius, J. Comp. Neurol. **29**:367, 1918.

33. Cleveland, D. W.: Personal communication to the authors; work to be published.

Stimulation of the Superior Cervical Sympathetic Ganglion Produces Pain.—In a series of ten normal cats we have been able to produce undoubted evidences of pain on stimulation of the superior cervical ganglion with a faradic current. The animals, which were under light ether or ethyl carbonate (urethane) anesthesia, struggled, cried out

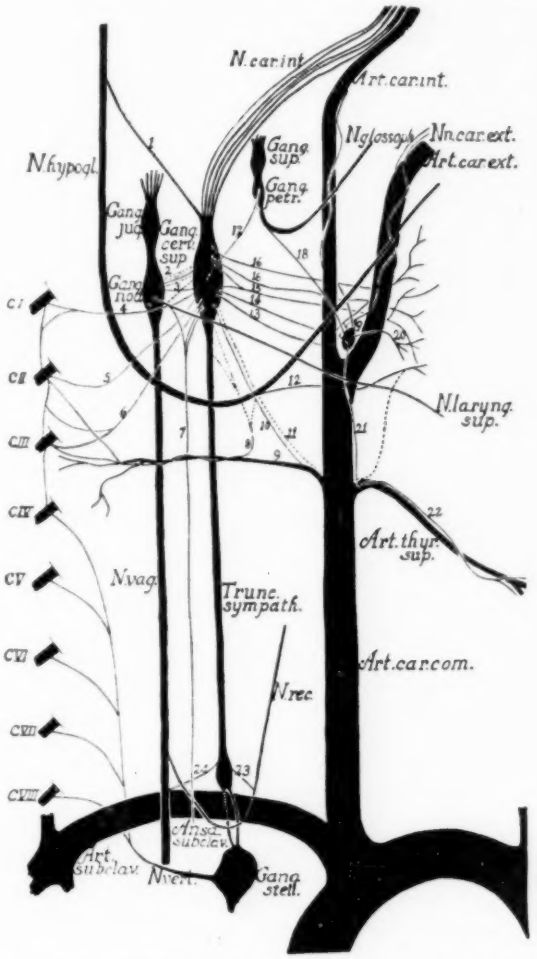

Fig. 1.—Diagram of the anatomy of the cervical sympathetic nervous system of the cat. (After Ranson and Billingsley.)

and showed violent tail wagging movements during the period of stimulation. This response occurred irrespective of whether or not the trunk was intact or severed below the ganglion (fig. 3). In every experiment care was exercised to hold the ganglion up from the surrounding tissues to prevent a misinterpretation by spread of the current.

The response was just as pronounced when the branches of the ganglion to the ganglion nodosum of the vagus were intact as when they were severed. In fact, the superior cervical ganglion can be isolated from all of its medial and lateral branches, and direct stimulation of it will produce pain (fig. 4).

This result is experimental corroboration of the evidence reported by Frazier, Peet and Foerster referred to previously. The interpre-

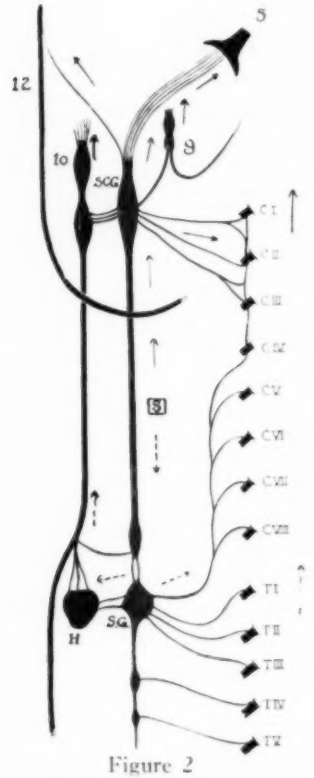

Figure 2

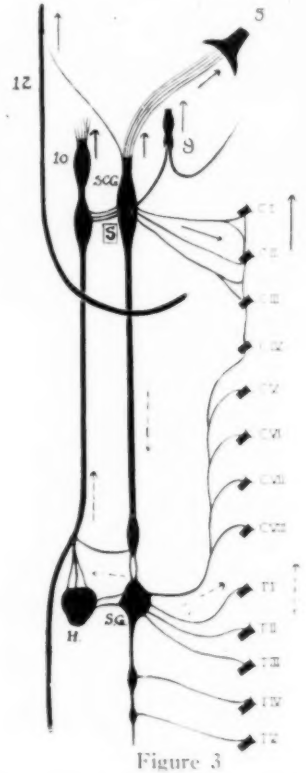

Figure 3

Fig. 2.—Diagram to illustrate the possible pathways for the transmission of impulses from stimulation of the trunk of the cervical sympathetic chain. No evidence of pain was produced.

Fig. 3.—Stimulation of the superior cervical sympathetic ganglion produced pain. The diagram illustrates possible pathways.

tation of the production of this pain was subjected to further experimental analysis. The possible pathways to be investigated were: through the posterior roots of the cervical spinal nerves, antidromic fibers in the anterior roots of the cervical spinal nerves and by a mechanism that is mediated finally through the cranial nerves.

Stimulation of the Superior Cervical Ganglion After Section of the Anterior Spinal Roots Produces Pain.—The first eleven anterior spinal roots were sectioned intradurally on one side in a group of five animals. These operations were done several days or weeks before the stimulation experiments were performed. The posterior roots were left intact, and their function was established by the presence of response to the ordinary forms of somatic sensory stimulation.

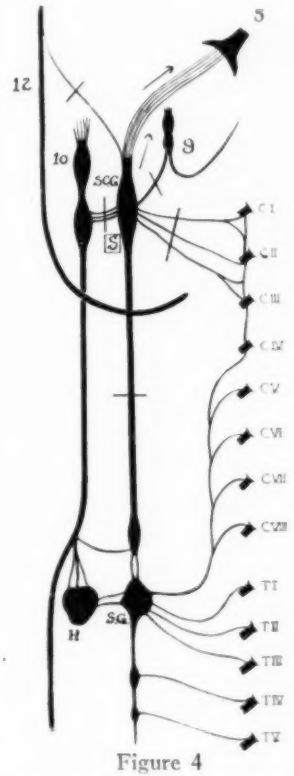

Figure 4

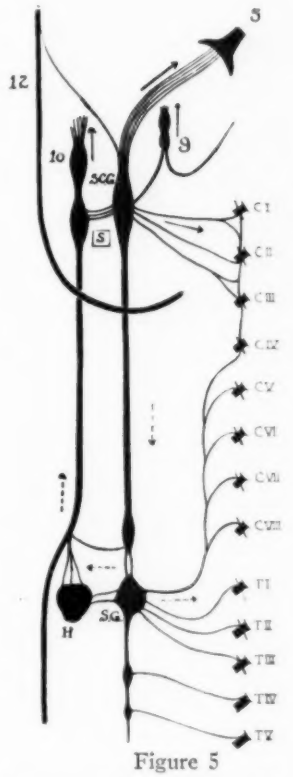

Figure 5

Fig. 4.—Stimulation of the superior cervical sympathetic ganglion produced pain after all of its branches except those to the carotid plexus were severed.

Fig. 5.—Stimulation of the superior cervical sympathetic ganglion produced pain after the anterior roots of the first eleven cervical anterior roots were sectioned.

In each of the animals direct stimulation of the superior cervical ganglion produced evidences of pain as unmistakable as those found in the preceding group of experiments. The responses were of equal intensity to those produced on the opposite normal control side (fig. 5).

Stimulation of the Superior Cervical Ganglion After Section of the Posterior Spinal Roots Produces Pain.—In another group of seven animals, the first twelve to fifteen posterior spinal roots were sectioned

intradurally. After these animals had been allowed to recover from the operation, the superior cervical sympathetic ganglion was exposed and stimulated with a faradic current. Again the animals struggled, cried out and showed vigorous tail wagging movements which were evidence of a painful response as marked as on the normal side (fig. 6).

Stimulation of the Superior Cervical Ganglion After Section of the Anterior Spinal Roots and the Posterior Root of the Trigeminal Nerve

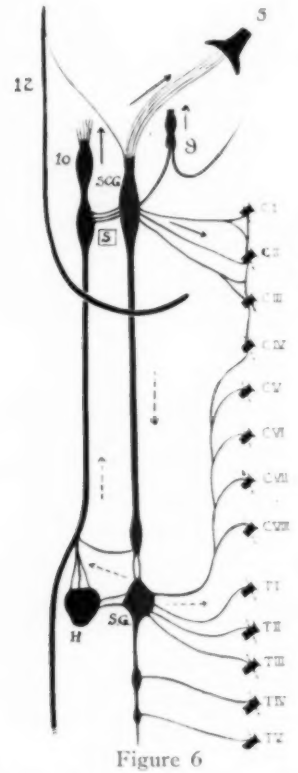

Figure 6

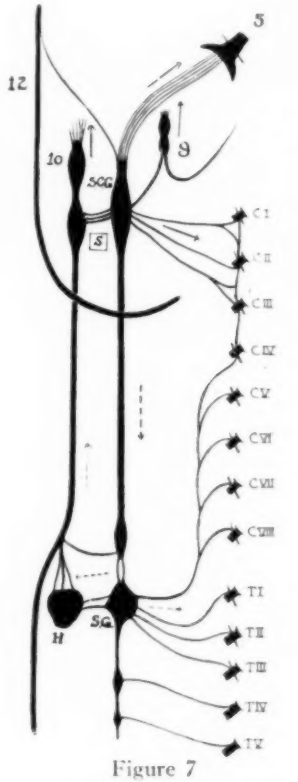

Figure 7

Fig. 6.—Stimulation of the superior cervical sympathetic ganglion produced pain after the posterior roots of the first fifteen cervical spinal nerves were sectioned.

Fig. 7.—Stimulation of the superior cervical sympathetic ganglion produced pain after the posterior root of the trigeminal nerve and the anterior roots of the first eleven cervical spinal nerves were sectioned.

Produces Pain.—In a group of three animals, the first ten anterior spinal roots were sectioned on the left side, leaving the posterior spinal roots intact. Several days later, the trigeminal posterior root was sectioned intracranially on the same side. After a period of recovery from this second operation had elapsed, the superior cervical ganglion

was exposed and stimulated with the faradic current. In all of the animals we obtained lateral movements of the head, crying out, struggling and movements of the tail. These responses were not as marked as on the normal side. They persisted in spite of section of the cervical sympathetic trunk below the superior cervical ganglion (fig. 7).

Stimulation of the Superior Cervical Ganglion After Section of the Posterior Spinal Roots and the Posterior Root of the Trigeminal Nerve

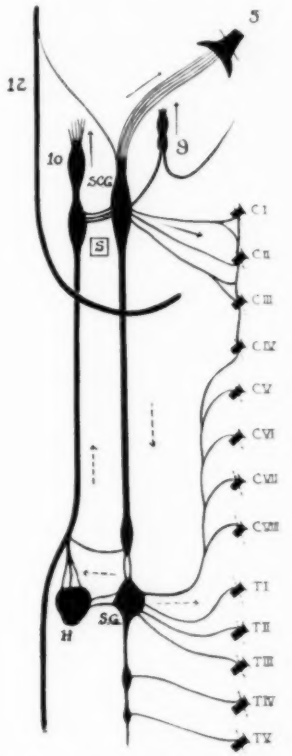

Fig. 8.—Stimulation of the superior cervical sympathetic ganglion did not produce pain after the posterior root of the trigeminal nerve and the posterior roots of the first fifteen cervical spinal nerves were sectioned.

Did Not Produce Pain.—In a group of four animals, the first twelve posterior spinal roots were sectioned bilaterally. At a subsequent operation the posterior root of the trigeminal nerve was sectioned intracranially. Several days later, the superior cervical ganglia were exposed and stimulated with a faradic current.

There were no evidences of pain when the ganglion was stimulated on the side operated on. Stimulation of the ganglion on the opposite side, on which the posterior spinal roots alone had been sectioned, gave definite and marked evidences of pain (fig. 8).

COMMENT

We believe that the anatomic evidence that there are no afferent sensory pathways in the cervical sympathetic trunk is fundamentally sound. It remains, therefore, to explain the very definite painful responses that are obtained by direct stimulation of the superior cervical ganglion in animals and in man.

In the presence of an intact cervical sympathetic trunk it might be possible for the stimulus to pass downward in the chain to the stellate ganglion and to be transmitted through postganglionic fibers through the gray rami to the spinal cord, in which these impulses might pass centrally to be appreciated as pain. The fact that stimulation of the trunk itself fails to produce pain and that section of the trunk below the superior cervical ganglion does not abolish the painful response speaks against such a pathway.

Since there are no preganglionic fibers in the cervical sympathetic trunk, it is evident that stimulation of the superior cervical ganglion produces pain by the stimulation of postganglionic efferent fibers. These impulses may be transmitted into the spinal cord through the posterior spinal roots or antidromically over the anterior spinal roots, since there are definite connections between the first three cervical nerves and the superior cervical ganglion in the cat. To avoid any error in the number of cervical spinal nerves with which the ganglion is connected we severed a larger number of anterior or posterior roots than the accepted anatomic facts might indicate. Such a pathway for the transmission of these painful impulses does not seem possible as the result of our experiments. It will be remembered that stimulation of the superior cervical ganglion produced pain after section of either the anterior or the posterior spinal roots.

It is an anatomic fact that the major part of the fibers from the superior cervical ganglion join the trigeminal nerve by way of the carotid plexus and are distributed through it to the structures of the head and face. In keeping with this fact we found that only after intracranial section of the trigeminal nerve and in the presence of section of the posterior roots were we able to abolish pain produced by stimulation of the superior cervical ganglion.

The failure to relieve certain atypical neuralgias by combined section of the sensory root of the fifth nerve and the superior cervical ganglion only points to the mass of clinical and experimental evidence which shows that the ordinary sensations of pain, touch and temperature are conducted centrally through the peripheral and central pathways of the trigeminal nerve and that deep pressure pain sensibility

is transmitted by the seventh cranial nerve (Spiller,[34] Ivy and Johnson,[35] Maloney and Kennedy,[36] Davis [37] and Gerard [38]). Davis offered evidence to show that the fibers that convey this type of deep sensibility in the face originate in the geniculate ganglion of the facial nerve and enter the brain stem by way of the sensory portion of that nerve. It is possible, therefore, that other sympathetic ganglia in connection with other cranial nerves may subserve a like function.

We believe, therefore, that stimulation of the superior cervical sympathetic ganglion produces an effect that is carried by way of postganglionic efferent fibers to the structures innervated by the sympathetic fibers. These efferent impulses produce an effect on the skin and other structures the exact nature of which we are unable to state. It is possible that it is linked with the sympathetic innervation of the blood vessels and that a metabolite is liberated which in turn stimulates the ordinary sensory nerve endings of the fifth nerve. This impulse is then transmitted centrally and is recognized as pain. The relief of pain of visceral disease by blocking or severing the intercostal and abdominal nerves is of great interest in this respect.

CONCLUSIONS

1. Stimulation of the superior cervical sympathetic ganglion produces pain in animals.

2. The appreciation of this pain is effected by the stimulation of efferent sympathetic fibers, the results of which in turn stimulate ordinary accepted sensory pathways in the cranial nerves.

3. Further evidence is offered that there are no antidromic sensory fibers in the cervical spinal anterior roots.

ABSTRACT OF DISCUSSION

DR. H. A. WOODS, Iowa City: In the cases in which the trigeminal sensory root was cut, was the pain perceived through one of the other cranial nerves?

DR. LOYAL DAVIS, Chicago: No doubt, Dr. Woods has referred to the patients who complained of pain after section of the trigeminal sensory root and the cervical sympathetic chain. In such patients our explanation for the presence of pain would be that other cranial nerves, such as the facial, which are known to convey pressure pain sensation, transmit the painful impulses of which the patients complain.

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34. Spiller, W. G.: Tumor of the Gasserian Ganglion, Am. J. M. Sc. **136**:712, 1908.

35. Ivy and Johnson: Preservation of Deep Sensibility of the Face After Destruction of the Fifth Nerve, Univ. Pennsylvania M. Bull. **20**:35, 1907.

36. Maloney, W. J., and Kennedy, R. F.: The Sense of Pressure in the Face, Eye and Tongue, Brain **34**:1, 1911.

37. Davis, Loyal: The Deep Sensibility of the Face, Arch. Neurol. & Psychiat. **9**:283 (March) 1923.

38. Gerard, M. W.: Afferent Impulses of the Trigeminal Nerve, Arch. Neurol. & Psychiat. **9**:306 (March) 1923.

LEAD POISONING IN CHILDREN

THE CEREBRAL MANIFESTATIONS *

CHARLES F. McKHANN, M.D. †
BOSTON

In 1926, there was published from this clinic (the Infants' and Children's Hospital) a report of a series of cases of lead poisoning in children, with a review of the literature and a discussion of the diagnosis and treatment with special reference to the encephalitic types of lead intoxication.[1] Since that time, cases of lead poisoning in infants and children have been encountered with increasing frequency; knowledge of the organic and functional changes produced by the metal has increased, and a number of clinical features have been observed that were not presented in the earlier paper.

Lead poisoning is seen occasionally in infants and children from the prolonged use of lead nipple shields [2] or from the ingestion of water containing lead; also lead is reported to have been obtained from face powder containing lead used by the child's mother; [3] however, the most common cause of the ingestion of lead appears to be the habit of small children of chewing paint from toys, cribs or woodwork of the house.[4] If the ingestion of lead paint continues for any considerable time, symptoms of intoxication result. True perversion of the appetite, so-called pica, appears to develop in some children and, in addition to paint, sand, coal, cloth or hair may be ingested. Mentally defective and highly neurotic children are prone to show evidences of pica; bizarre

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† From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals.

* Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

1. McKhann, C. F.: Lead Poisoning in Children, Am. J. Dis. Child. **32**:386 (Sept.) 1926.

2. Wilcox, H. B., and Caffey, J. P.: Lead Poisoning in Nursing Infants: Report of Two Cases Due to Use of Lead Nipple Shields, J. A. M. A. **86**:1514 (May 15) 1926.

3. Hirai, I.: Meningism in Sucklings in Japan from Lead Poisoning, Arch. Pediat. **44**:137, 1927. Fukushima, M., and Matsumoto, H.: Statistics of Two Hundred and Ninety-Eight Cases of Infantile Lead Poisoning, Orient. J. Dis. Infants **3**:27, 1928.

4. Ruddock, J. C.: Lead Poisoning in Children with Special Reference to Pica, J. A. M. A. **82**:1682 (May 24) 1924.

appetites may develop in anemic children, and children harboring certain intestinal parasites are notorious in this respect. However, of the children with lead poisoning who have come under the observation of my associates and myself, many do not fit into any of these groups, but appear to be normal children who have merely a pernicious habit.

SYMPTOMS

The early manifestations of lead poisoning are those referable to the gastro-intestinal tract—anorexia, constipation and colic—associated in most cases with a variable degree of anemia. More serious symptoms are those referable to the central nervous system—vomiting, frequently of a projectile character, visual disturbances, delirium, stupor, coma or convulsions. These neurologic evidences of lead poisoning often are associated with an elevation of the arterial blood pressure, choking of the optic disks or even separation of the cranial sutures. If death occurs, it usually follows a period of coma or severe convulsions. While the heart continues to beat for some minutes, the respirations cease, apparently because of central respiratory involvement. The clinical picture of lead encephalitis was described by Tanquerel des Planches in 1839.[5]

The cerebral manifestations of lead poisoning appear to be due to extreme cerebral edema resulting from the deposition of lead in the brain. This marked cerebral edema was observed by Chvostek in 1897, and has been produced experimentally in laboratory animals by Weller.[6] Chvostek's patient was a young girl in whom lead poisoning of the encephalitic type developed, characterized by headache, vomiting, slow pulse, coma, choked disks and vasomotor disturbances, ending in death. At necropsy the meninges were clear, the whole brain was intensely swollen, the medulla was pressed into the spinal canal, the convolutions were flattened, and the ventricles were small. More recent necropsy observations thoroughly confirm this early description.

If the patient survives a severe encephalitic stage, permanent cerebral sequelae may remain, among them blindness, cerebral palsy, cerebral atrophy and degeneration, internal hydrocephalus, epileptiform seizures and mental deficiency, all presumably the result of impaired circulation in the brain during the prolonged state of increased intracranial tension.

The development of encephalitic manifestations is more frequent in children than in adults, whereas the type of neurologic involvement

5. Tanquerel des Planches: Lead Diseases, translated by S. L. Dana, Boston, Tappan, Whittemore & Mason, 1850.

6. Weller, C. V.: Tolerance in Respect to Meningocerebral Manifestations of Acute and Subacute Lead Poisoning: Experimental Production, Arch. Int. Med. **39**:45 (Jan.) 1927.

commonly seen in adults, peripheral neuritis, has been encountered relatively infrequently in children.

The incidence of lead poisoning in this clinic in the past six years, with the frequency of encephalitic types, the fatality and the occurrence of sequelae, is shown in the accompanying table.

Lead Poisoning in Children in the Boston Infants' and Children's Hospital

Cases of lead poisoning	40
Encephalitis	24
Deaths	9
Permanent injury presumably due to encephalitis	5
Suspected cases, unproved	8

DIFFERENTIAL DIAGNOSIS

Lead encephalitis must be distinguished from other forms of encephalitis, from brain tumor and abscess, from tuberculous meningitis and from meningism. The neurologic signs alone are seldom adequate for the differentiation, as the signs of lead encephalitis are apparently pathognomonic, not of lead poisoning, but only of increased intracranial pressure. Lead neuritis, of course, must be differentiated from other forms of peripheral neuritis.

The diagnosis of lead poisoning is usually made from the correlation of the history and physical examination with certain laboratory data. In early infancy the prolonged use of a lead nipple shield and in childhood a history of pica, together with the development of the train of symptoms already described, lead to a consideration of lead poisoning. Lead lines in the gums are relatively uncommon in children, but when present are good evidence of lead intoxication. (A lead line consists of a deposit of black granules of lead sulphide in the capillaries at the gum margin. This deposit is formed through the chemical precipitation of lead from the circulation by the action of sulphides produced from the decay of food matter between the teeth. Less than 20 per cent of the patients at this clinic showed a lead line.)

The presence in the blood of erythrocytes with basophilic stippling has been widely considered diagnostic of lead poisoning. This laboratory observation is of value if one bears in mind that, although perhaps most common in lead poisoning, it is present in other conditions, notably certain blood disorders, and that, furthermore, it may be absent from the blood of patients who still harbor in their bodies large amounts of lead. A nonspecific observation in the blood of some importance is a definite increase in the percentage of reticulated red cells. The presence of lead in small amounts in the stools and urine of infants and children has been shown to be of common, almost normal, occurrence,[7]

7. Kehoe, R. A.: Personal communication.

so that demonstration of lead in the excreta must be quantitative if one is to use this observation as evidence of poisoning. Quantitative measurement of lead in the excreta, properly appraised, is, however, a most satisfactory proof of lead poisoning.

A recent diagnostic observation that promises to be of considerable value is the roentgenologic sign of the presence of lead in the bones, described almost simultaneously by Park [8] and by Vogt.[9] The sign to

Fig. 1.—Dense bands at the growing ends of the long bones observed in a child with lead poisoning. The picture at the right shows the long bones of the same patient two months later. Note the greater breadth of the bands.

which these authors called attention is a dense band found in roentgenograms at the growing ends of the long bones or at the growing margins of the flat bones (fig. 1). Vogt also pointed out the occasional

8. Park, E. A.; Jackson, E., and Kajdi, L.: Shadows Produced by Lead in the X-Ray Pictures of the Growing Skeleton, Am. J. Dis. Child. **41**:485 (March) 1931.

9. Vogt, E. C.: A Roentgen Sign of Plumbism, Am. J. Roentgenol. **24**:550, 1930.

discovery of dense flecks in films of the abdomen, presumably particles of ingested lead in the intestinal tract. This, of course, is observed only in children who have chewed paint recently (fig. 2).

Chemical analysis of the dense bands at the growing ends of the long bones demonstrated that lead was present in these bands in several times the concentration found in the shaft, and that the calcium was actually diminished in amount, indicating that lead instead of calcium

Fig. 2.—Roentgenogram of the abdomen of a patient who had recently ingested lead paint. Note the opaque flecks in the pelvic region. These flecks are presumably unabsorbed lead in the intestinal tract.

is laid down to some extent in these heavy bands. The intensity and breadth of the bands vary with the age and size of the child, the duration of the ingestion of lead, the amount of the metal absorbed and the rate of growth of the bones. If the bones are reexamined at intervals following the removal of the source of lead, the bands become progressively broader and less distinct, owing to the gradual elimination of the metal.

Although this roentgenologic sign seems to be of considerable value, it is apparently not pathognomonic of the presence and deposition of lead. Occasionally, similar pictures have been observed following the ingestion or injection of other metals and salts.[10]

However, the roentgenologic sign has led to the discovery of a number of patients, subsequently proved to have cases of lead poisoning, whose presenting symptoms did not occur in the typical sequence ordinarily observed in lead poisoning; in several instances such lines were found in patients who were free from symptoms. Thus, confirmatory evidence has been added to the knowledge of the manner of deposition of lead in the body, which is briefly as follows:

Lead, after absorption from the gastro-intestinal tract, is carried in the blood in a soluble form until it is deposited in certain organs and tissues. Aub and his co-workers[11] have contributed accurate measurements of the relative amounts of lead in the various organs of the body; the liver, brain and skeleton bind most of the metal. Eventually the lead disappears from the circulation, being deposited in the bones in an inert form in much the same manner as calcium is laid down. Accompanying the removal of lead from the blood are a fall in the number of stippled red blood cells and a gradual cessation of symptoms. This condition I refer to as latent lead poisoning. The patient's body contains lead in dangerous amounts, bound in inert form in bone—in children in the growing ends of the bones—and producing the lead line already described. From the bones lead is gradually mobilized in small amounts and redeposited or excreted. This process may go on for years without the production of any symptoms in the patient, until most of the lead has left the body. Under certain circumstances, notably in the presence of an acute febrile attack or of severe acidosis, large amounts of lead may be released from the bones into the circulation and serious symptoms of lead intoxication may ensue. The deposition of lead in the bones may be hastened by the use of a diet high in calcium, together with the administration of viosterol or cod liver oil or exposure to sunlight. Removal of lead from the bones, so-called deleading, may be accomplished in some measure by the induction of acidosis or alkalosis, or by the administration of parathyroid hormone.[12] Because of the danger of aggravating the

10. Phemister, D. B.: The Effects of Phosphorus on Growing Normal and Diseased Bones, J. A. M. A. **70**:1737 (June 8) 1918. Vogt, E. C.: Roentgenologic Diagnosis of Lead Poisoning in Infants and Children, ibid. **98**:125 (Jan. 9) 1932.

11. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Medicine **4**:1 (Feb.-May) 1925.

12. Hunter, D., and Aub, J. C.: Lead Studies: Effect of Parathyroid Hormone on Excretion of Lead and of Calcium in Patients Suffering from Lead Poisoning, Quart. J. Med. **20**:123, 1927.

symptoms in children by reason of the release of lead into the circulation, my associates and I have largely abandoned this deleading process.

The neurologic manifestations of lead poisoning usually subside without serious consequences if the ingestion of lead is stopped, and the removal of lead from the circulation and its deposition in inert form in the bones can be hastened, as described, by the use of a diet high in calcium, together with the administration of cod liver oil or viosterol, to accelerate the laying down of new bone. However, in the more severe cases of encephalitis, greater difficulties are encountered. The rate of removal of lead from the brain appears to be slow and not readily influenced by therapy. In these severe cases the control of increased intracranial tension becomes of paramount importance.

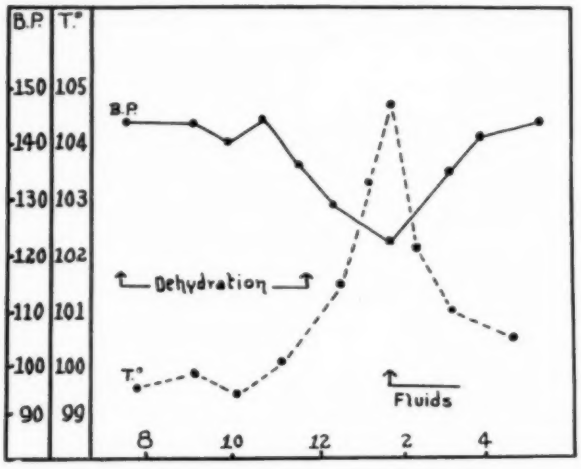

Fig. 3.—Dehydration by hypertonic solutions in lead poisoning and in epidemic encephalitis. The cerebral manifestations of lead poisoning, due presumably to intense cerebral edema and associated with an elevation of the blood pressure, do not respond readily to the intravenous injection of hypertonic solutions. If hypertonic solutions are administered in amounts sufficient to lower the blood pressure and to cause cessation of cerebral symptoms, dehydration fever becomes a problem.

Attempts to relieve the cerebral edema by hypertonic solutions have met with little success. Dehydration of the whole body by means of the injection of hypertonic solutions has been carried to the point of the appearance of dehydration fever before the relief of cerebral symptoms has become manifest. This is exemplified in figure 3. In the experience of my associates and myself, the repeated administration of small doses of magnesium sulphate intramuscularly in 25 per cent solution serves to lower, temporarily, the blood pressure and to relieve the symptoms of cerebral edema (fig. 4). The action of the drug seems

to be due in large measure to the depressing and relaxing effect of the magnesium ion. Although it has been possible to control the symptoms even in very severe cases by this method of treatment, unfortunately, the development of deplorable sequelae has not been prevented. (In view of the serious outlook in these severe cases, one feels justified in considering more radical procedures, such as decompression, as means of controlling the tremendously increased intracranial tension.)

The following case illustrates the course of a severe form of lead encephalitis.

REPORT OF A CASE

F. M., a boy, aged 22 months, who was admitted to the hospital in March, 1928, was said to have been of normal mental and physical development until 18

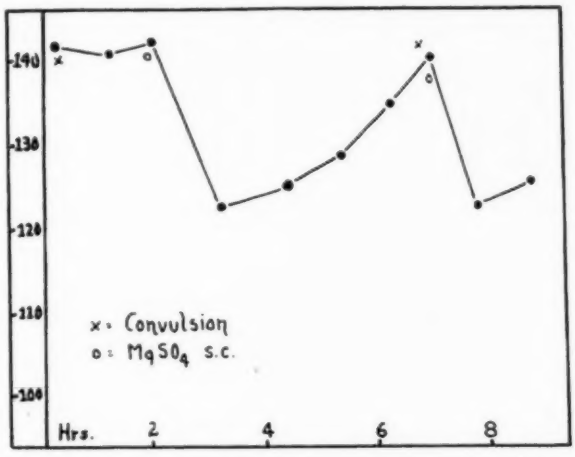

Fig. 4.—The control of elevated blood pressure and of cerebral symptoms of lead poisoning by intramuscular injection of magnesium sulphate. As indicated, the injections must be repeated at intervals of from four to six hours.

months of age. At that time he began to chew the paint from the woodwork of the house and from toys. This habit persisted, and in a few weeks he began to suffer from constipation, anorexia and occasional attacks of vomiting. A few days prior to entry to the hospital, the vomiting increased in frequency; the child became apathetic and irritable, and finally convulsions developed.

On admission, examination revealed that he was well developed, undernourished and apathetic. Examination of the blood showed a high percentage of stippled red cells. The day following admission, generalized convulsions developed, which recurred at frequent intervals for several days. Throughout this time the spinal fluid remained clear, under increased pressure and with increased globulin. The arterial blood pressure was considerably elevated. The optic disks showed choking of marked degree, and in the course of three or four days the fontanel enlarged and the sutures of the skull opened widely. The convulsions were controlled by the use of magnesium sulphate in 25 per cent solution, given intramuscularly.

As the symptoms of cerebral edema subsided, blindness was noted, as well as weakness and spasticity of the left side of the body. These sequelae persisted, and, in addition, throughout the three succeeding years, the patient experienced recurrent mild convulsive seizures. Two years after the acute lead encephalitis, a ventriculogram showed considerable cortical atrophy on the right side of the brain (fig. 5).

Lead induced the original attack, but at the present time the child harbors very little lead in his body. The permanent injuries are thought to be due to impairment in the circulation of the brain produced by the extreme edema present throughout the acute encephalitic stage.

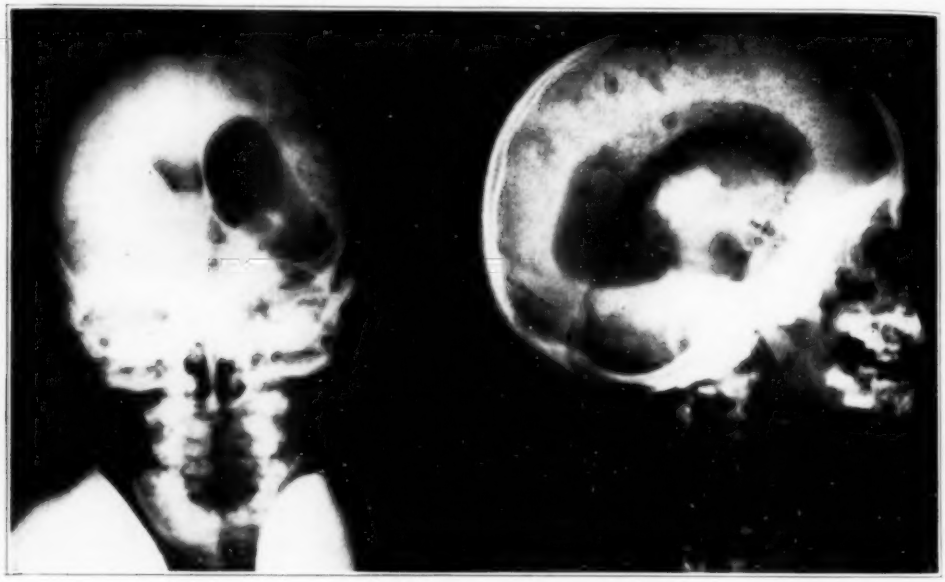

Fig. 5.—Encephalograms of a patient who survived an acute, severe lead encephalopathy, but was left with one-sided convulsions and hemiparesis caused by the extensive cortical atrophy evident in the pictures.

SUMMARY AND CONCLUSIONS

Lead poisoning in children produces a severe and dangerous form of cerebral involvement, the symptoms of which apparently are dependent on the development of an extreme cerebral edema. Less frequently there is encountered the peripheral neuritis commonly observed in adults with lead poisoning. Children who survive a severe lead encephalitis are frequently left with permanent neurologic disorders. The early diagnosis of lead poisoning based on a carefully taken history and physical examination, confirmed by roentgenologic and laboratory data, should lead to the institution of active therapy, which may result

in the prevention of the development of serious neurologic manifestations. In the presence of the acute, severe cerebral manifestations, attention must be directed toward the control of greatly increased intracranial tension.

ABSTRACT OF DISCUSSION

DR. K. L. BLACKFAN, Boston: I appreciate the opportunity to enter the discussion even though there is so little that I can add to what Dr. McKhann has said. From a diagnostic point of view one might, perhaps, emphasize the infrequency with which, in children who are not subject to dental caries or pyorrhea, the lead line in the gums is of aid in making the diagnosis.

I might, perhaps, stress the fact that in the last ten years our knowledge as to the various causes of convulsions in young children has increased tremendously. Plumbism with cerebral manifestations, up to ten years ago, was practically unknown to pediatricians, and the knowledge secured from the field of chemistry has increased our information in relation to the cause of convulsions in tetany. At the onset of acute infectious diseases in which one sees convulsions, there is pathologic evidence to indicate that infection with the streptococcus, the filtrable viruses and other organisms bring about, rather rapidly, an acute cerebral edema. As Dr. McKhann has illustrated to you, in treating these children with cerebral symptoms — convulsions, coma, blindness, vomiting, and so forth — with magnesium sulphate, we are now undoubtedly approaching the therapeutic situation with a much more clear understanding than we have had in the past.

DR. TEMPLE FAY, Philadelphia: I have been much impressed with Dr. McKhann's presentation. Two points in his problem have presented themselves to us. I might add the experience that we have had in overcoming the difficulty encountered in controlling the cerebral edema.

A year and a half ago, after closure of a meningocele, secondary hydrocephalus developed in a 2 weeks old infant, requiring daily tapping of the ventricles. Even with this drainage of the spinal fluid, the head rapidly enlarged. We were forced to give a dry diet, or a modified dry diet, to the baby. We were fortunate enough to obtain the cooperation of a pediatrician while placing this 5 weeks old baby, who had a progressive communicating type of hydrocephalus, on a 12 ounce (360 cc.) mixture. Feedings consisted of cereal, mashed potatoes, mashed bananas and bread broken in milk. We were told that it was impossible to feed a 5 weeks old child on a 12 ounce diet, such as I have indicated. The child is 1½ years old now, is within 2 pounds (0.9 Kg.) of its normal weight, and has normal mentality. After giving the diet prescribed, the head enlarged only 1 cm. to the present time, as compared with 4 cm. before the diet was given. The interesting thing is that the biparietal measurements decreased 7 cm. during the first three weeks that the child was on the diet and on restriction of fluid. At the seventh month, the fluids were increased to 36 ounces (1,260 cc.), and the head enlarged 1.5 cm. We have had several cases of so-called status epilepticus of the edematous type, and we have not hesitated to place these children on a low fluid intake, with the necessary caloric value obtained by the addition of solids. Apparently, they get along very well until warm weather is encountered, and then with the added loss of fluid through the skin, which is greater than the fluid intake, there may be a rise in body temperature, and it becomes necessary to sponge the infants or to give them more fluids.

During the last year and a half, we have had eleven infants who have been placed on the routine restriction of fluids, and the treatment has proved very effectual, at least so far as the hydrocephalic symptoms are concerned.

DR. N. W. WINKELMAN, Philadelphia: Was any pathologic study made in these cases? I think the term "encephalitis" is a misnomer. I have, perhaps, been foolish enough to try to coin a new term for cases of this sort. I have named them "encephalosis." I have had occasion to examine such cases, and have found that the edema affects the entire cellular mechanism of the nervous system, producing such marked swelling, particularly in the cells of the small capillaries, that there result areas of degeneration entirely similar to those that Cobb has called "areas of devastation."

DR. HENRY A. RILEY, New York: Do you use any sodium thiosulphate at all?

DR. MCKHANN: No. We have not used sodium thiosulphate.

I had intended to say that we feel that permanent cerebral injuries following lead poisoning are due to anemia of the brain produced by the intense edema. I do agree with the last speaker that the term "encephalitis" is perhaps a poor term, and were the time longer I might enlarge and say that I think a great many of the terms describing conditions in which the symptoms are produced by cerebral edema had better be changed.

In speaking of uremia associated with acute hemorrhagic nephritis, we prefer the term "cerebral manifestations of acute hemorrhagic nephritis," because the symptoms appear to be produced in large measure by cerebral edema. As regards the term "encephalosis" for cerebral signs of systemic disease, I hope that the persons who have produced the term know more about the pathology of encephalosis than we do about nephrosis.

ALTERATIONS IN THE STRUCTURE OF THE SELLA TURCICA

AS REVEALED BY THE ROENTGEN RAY *

KARL KORNBLUM, M.D.
PHILADELPHIA

In the routine study of patients with suspected intracranial disease, roentgenologic examination of the head is now generally recognized as an important and valuable aid to diagnosis. Among the various roentgen manifestations of intracranial disease, the changes encountered in the sella turcica are unquestionably the most significant. Alterations in this structure are among the most frequent abnormalities of the skull to be seen on the roentgenogram. It is for this reason that a thorough knowledge of the roentgenology of the sella turcica is essential for the proper interpretation of roentgenograms of the head. It is needless to say that one must be thoroughly familiar with the appearance of the normal sella and be able to recognize its many normal variations before one can judge of the abnormal.

TECHNIC

The roentgenologic technic employed in examinations of the sella turcica is a matter of considerable importance. While the technic used by various roentgenologists may differ somewhat in certain details, the same basic principles are no doubt universally adhered to. The technic employed at the University Hospital has been in use with satisfactory results for many years. Figure 1 illustrates the so-called pituitary or measuring film from which measurements of the pituitary fossa are obtained. This should be a true lateral view of the sella. Great care must be taken that no rotation of the head in any direction occurs. A true lateral view is best obtained by having the patient lie on his back, with an 8 by 10 film in a cassette placed along one side of the head and the roentgen tube directed from the opposite side. The film target distance is 36 inches (91.4 cm.), as films made at this distance give much less distortion than when shorter distances are used. Maintaining a constant distance is, of course, essential when comparative measurements are employed, as is done in determining the size of the pituitary fossa. The central beam of the roentgen ray is made to pass through a point 1 inch (2.5 cm.) in front and ½ inch (1.2 cm.) above the tragus. This places the sella turcica in the center of the exposed area. A small cone is used to secure greater detail. The exposure factors are 80 kilovolts, 10 ma. and from

* Submitted for publication, July 29, 1931.

* From the Department of Roentgenology, Hospital of the University of Pennsylvania.

* Read by invitation before the Philadelphia Neurological Society, April 24, 1931.

three to five seconds, depending on the size of the head. While this film constitutes the principal source from which information regarding the sella turcica is obtained, the routine examination of the sella, as well as of the head, includes a stereoscopic lateral view of one side of the skull. Frequently this gives information regarding the sella turcica that cannot be obtained from the flat film alone. Occasionally it is of advantage to make stereoscopic views of both sides of the head.

Figure 2 is a drawing made from the roentgenogram shown in figure 1. It depicts graphically the essential parts of the sella turcica and the immediately adjacent structures with which one is concerned in the detection of deformations of the sella. Briefly, these structures are: the pituitary fossa, bounded posteriorly by the dorsum sellae, which is surmounted by the posterior clinoid processes.

Fig. 1.—Roentgenogram of the sella turcica, lateral view. The so-called pituitary or measuring film from which the measurements of the pituitary fossa are obtained.

The anterior wall of the pituitary fossa terminates above in the tuberculum sellae, on either side of which is seen the anterior clinoid process. Both the anterior and posterior clinoid processes appear as single structures, because in the true lateral view they are superimposed on each other. Passing anteriorly from the tuberculum sellae are to be seen the ridges representing the floor of the anterior cranial fossa on either side. Below the floor of the pituitary fossa is the sphenoid sinus. A curved line, often crossing the sphenoid sinus, which passes upward and forward to terminate above the level of the anterior cranial fossa, represents the floor of the middle cranial fossa. Posteriorly, this curved line becomes lost in the superimposed mastoid and petrous portions of the temporal bone. Here can usually be seen the external auditory meatus. These various structures are usually readily recognized in roentgenograms of the sella turcica.

ANATOMIC DATA

Anatomic studies of the sella turcica have shown innumerable variations from the normal. Attempts have been made to classify the sella according to the shape of the pituitary fossa. The simplest of these classifications recognizes the oval, round or circular and flat types (fig. 3, nos. 1, 2 and 3). The first two are by far the most common, with the oval predominating in adults and the circular in children. According to Gordon and Bell,[1] the shape of the sella is of no significance, except in the flat type which is always found in small heads. Attention is directed to the variation in the size of the sphenoid sinus as shown in figure 3. In this series the sinus becomes progressively larger until in sella no. 4 it occupies the entire body of the sphenoid bone, extending up into the dorsum sellae, giving rise to the so-called

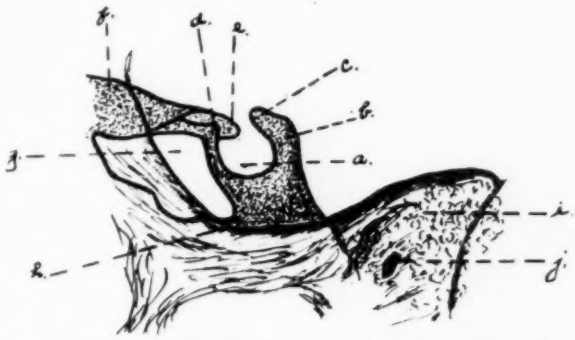

Fig. 2.—Drawing to show the important parts of the sella turcica and adjacent structures: *a*, pituitary fossa; *b*, dorsum sellae; *c*, posterior clinoid process; *d*, tuberculum sellae; *e*, anterior clinoid process; *f*, floor of anterior cranial fossa; *g*, sphenoid sinus; *h*, floor of middle cranial fossa; *i*, superimposed mastoid and petrous portions of the temporal bone, and *j*, external auditory meatus.

pneumatic dorsum. Because of this variation in size, it becomes difficult to estimate the degree of encroachment on the sinus by pituitary tumors, and attempts to use this factor as a criterion in determining the extent of enlargement of the pituitary fossa have proved valueless.

Figure 4 shows four additional variants commonly seen in adults. Sella no. 5 presents a very large thick, plump dorsum, while no. 6, in contrast, is possessed of a small, thin dorsum. The latter is more frequently encountered. In no. 8 is seen an interesting and fairly common type, the so-called bridged sella. This is produced by a union of the anterior and posterior clinoid processes. Occasionally the middle clinoid process is present and takes part in the bridging, as in the case

1. Gordon, M. B., and Bell, A. L.: A Roentgenographic Study of the Sella Turcica in Normal Children, New York State J. Med. **22**:54, 1922.

shown in no. 8. Through the anterior foramen, formed by the anterior and middle clinoid processes, passes the internal carotid artery. Camp [2] placed the incidence of the bridged sella at 5.5 per cent. Claims have been made that the bridged sella is responsible for certain pituitary symptoms, especially pituitary headache, supposedly produced by a diminution in the size of the fossa, resulting in pressure on the pituitary gland. When one recalls the anatomic relationship of the anterior clinoid processes to the pituitary fossa and takes cognizance of the fact that they are well lateral to the fossa, one can see that bridging does not reduce the size of the fossa as it appears to do on the roentgenogram, and exerts no pressure on the normal gland. The bridged sella, therefore, is not considered of any clinical significance.

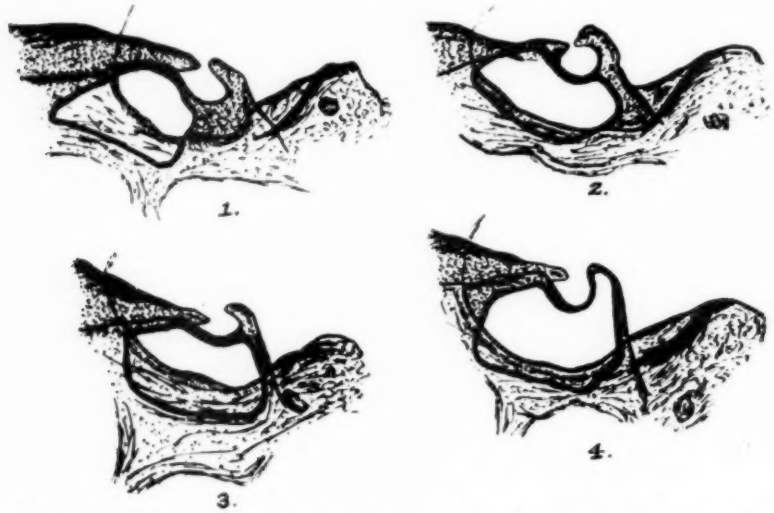

Fig. 3.—Variations in the normal adult sella turcica: *1*, oval type of pituitary fossa; *2*, circular type; *3*, flat type, and *4*, pneumatic dorsum sellae.

More intriguing and of more practical importance is the type of sella shown in no. 7. Here will be noted a very faint and indistinct dorsum sellae, one which frequently gives rise to the question as to whether or not it is of pathologic significance. Schüller [3] has called attention to the so-called senile atrophy of the sella turcica, but this type of dorsum is not confined to persons of advanced years. It may

2. Camp, John D.: The Normal and Pathologic Anatomy of the Sella Turcica as Revealed at Necropsy, Radiology **1**:65, 1923; The Normal and Pathologic Anatomy of the Sella Turcica as Revealed by Roentgenograms, Am. J. Roentgenol. **12**:143, 1924.

3. Schüller, A.: Roentgen Diagnosis of Diseases of the Head, St. Louis, C. V. Mosby Company, 1918.

be found at any age in adults. In seeking for a cause of this appearance, Dr. O. V. Batson, professor of anatomy in the Graduate School of Medicine, the University of Pennsylvania, was consulted. He gave a plausible explanation for this appearance. An attempt has been made to illustrate this in figure 5. Dr. Batson called attention to the fact that while the dorsum sellae is made up of cancellous bone, this bone contains numerous blood vessels, traversing the dorsum in all directions, making, in effect, an intra-osseous sinus. At times these vessels are few in number and small in size. In consequence, the trabeculae of the bone are numerous, thick and densely impregnated with calcium as shown in figure 5 *a*. For these reasons, such a dorsum casts a dense shadow on the roentgenogram. In contrast is the dorsum shown

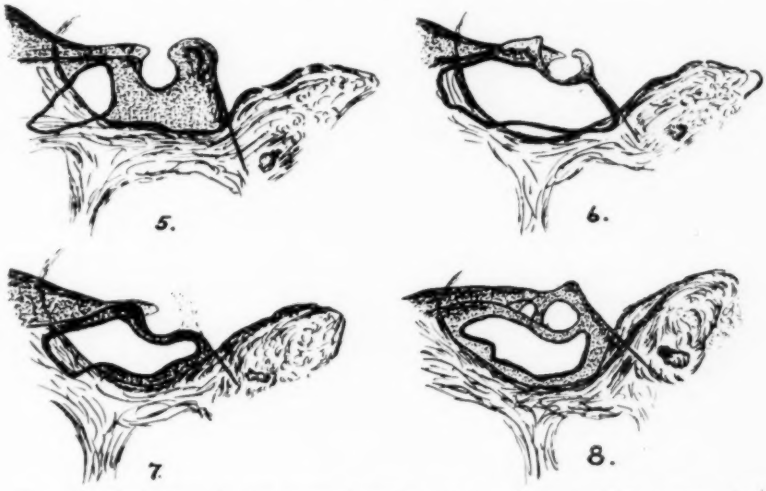

Fig. 4.—Variations in the normal adult sella turcica: *5*, thick, heavy dorsum sellae; *6*, small, thin dorsum; *7*, faint, indistinct dorsum, and *8*, the bridged sella.

in figure 5 *b*, in which the blood vessels are quite large and the bony trabeculae correspondingly few and thin. Such a dorsum gives rise to a faint, indistinct shadow, and unless the technical quality of the film is satisfactory, such a dorsum may appear to be entirely absent. Possibly the transmission of pulsations to these vascular channels of the dorsum from the sclerosed blood vessels of elderly persons results in erosion of the bony trabeculae, thus giving rise to the so-called senile atrophy of Schüller.

At times there is an actual atrophy of the dorsum sellae that cannot be attributed to any of the causes mentioned and that, at the same time, is possessed of no clinical significance. It is conceivable that intermittent periods of increased intracranial pressure occurring especially during childhood, unassociated with serious intracranial disease,

may give rise to varying degrees of atrophy of the dorsum. Such changes would, of course, be permanent, as regeneration of the dorsum probably never occurs. Such atrophy found subsequently may be misleading, especially if some intracranial disease is suspected. Great care, therefore, must be exercised in the proper evaluation of atrophy of the dorsum sellae.

In figure 5 *c* is to be seen a common appearance of the dorsum sellae. There are roughening and erosion of the posterior aspect of this structure. The line shown just behind the dorsum represents the dura mater. Dr. Batson called attention to the fact that this reflection of the dura, which ordinarily is attached rather firmly to the posterior aspect of the dorsum and body of the sphenoid bone and the adjacent basilar portion of the occipital bone, known anatomically as the clivus, is not infrequently separated from the clivus by a plexus of veins, com-

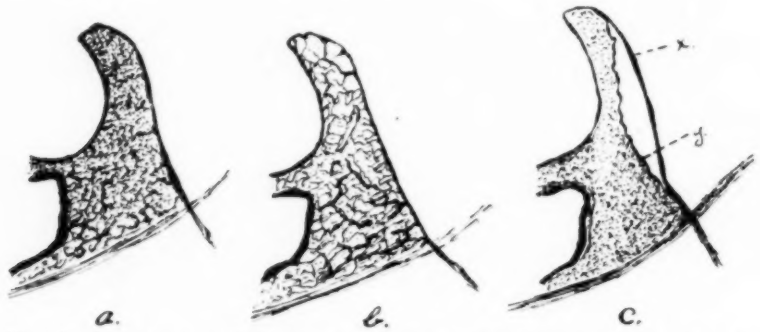

Fig. 5.—Drawings to illustrate the cause of the appearance of atrophy in the normal dorsum sellae: *a*, dorsum contains few blood vessels and much calcium; would appear as a dense shadow on the roentgenogram; *b*, dorsum contains many large blood vessels and very little calcium; would appear as a faint, indistinct dorsum; *c*, dura (*x*) separated from clivus (*y*) by plexus of veins, the so-called basilar sinus. Transmitted pulsations result in erosion of the posterior aspect of the dorsum sellae.

monly called the basilar sinus. This sinus is in free communication with the cavernous sinuses, and is drained by the bilateral inferior petrosal sinuses. With this basilar sinus numerous small vessels communicate from the underlying bone. Examination of anatomic specimens shows the numerous small openings through which these vessels pass. Pulsations transmitted from the adjacent brain to this plexus of veins and the branches from the bone are probably responsible for the atrophy and irregularity of the posterior aspect of the dorsum sellae. This appearance, therefore, is of no clinical significance.

In this connection it is well to call attention to the fact that the dura overlying the clivus is not infrequently calcified or, more correctly

speaking, ossified. As a matter of fact, any of the reflections of the dura attached to the anterior or posterior clinoid processes and even the diaphragma sellae may be ossified. This occurrence, while of no clinical importance, should not be mistaken for calcification in adjacent tumors or aneurysms.

The sella turcica of an infant or child is, as a rule, readily distinguished from that of an adult. Figure 6 shows the sella at various ages during infancy and childhood. The sella, as will be noted, is quite sturdy in appearance; the dorsum is thick and plump, the pituitary fossa is usually circular, and is proportionately smaller. With increase in age, the appearance of the sella approaches that of the adult, so

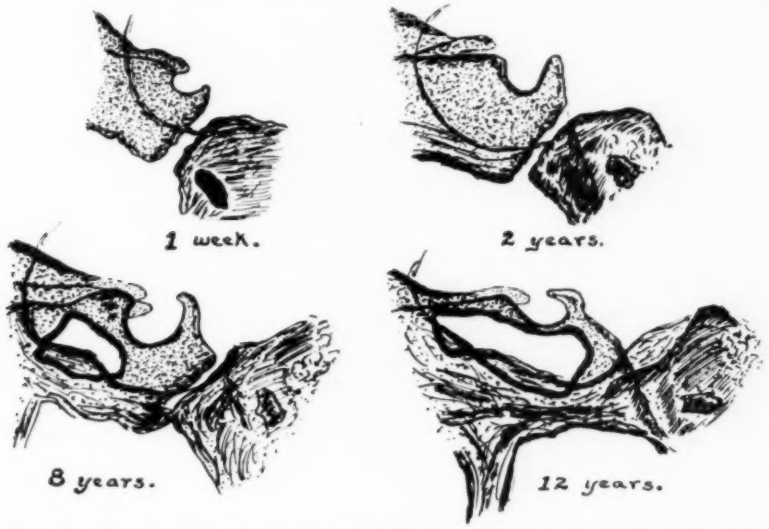

Fig. 6.—Appearance of the sella turcica at various ages during infancy and childhood.

that at about the age of 12 years it can no longer be distinguished from that of the adult. It will be noted that in infants the sphenoid sinus is absent. This sinus does not usually make its appearance until about the third year. Attention is called to the space on the roentgenogram separating the sphenoid bone from the mastoid and petrous portions of the temporal bone. This is a fissure, occupied by cartilage, which in reality separates the sphenoid from the basilar portion of the occipital bone and constitutes the basilar suture or spheno-occipital fissure. This suture does not close until about the eighteenth year, but in the roentgenogram is only occasionally seen beyond the eighth or tenth year. This and the other sutures of the skull are important in that their separation or widening during appreciable increases in intracranial pres-

sure often prevent such pressure from producing the characteristic changes in the sella turcica found in adults after closure of the sutures. This is one of the reasons that deformations of the sella occur much less commonly in children than in adults.

ALTERATIONS IN INTRACRANIAL DISEASE

In a consideration of the alterations in the structure of the sella turcica resulting from intracranial disease, there are three changes to which attention should be called. Since these are the ones most frequently encountered and unquestionably the ones of greatest importance, they may well be termed the cardinal changes in deformations of the sella turcica. These changes are illustrated in figure 7 and consist of: (1) atrophy of the dorsum, (2) erosion of the floor of the pituitary fossa and (3) increase in the size of the pituitary fossa. While other

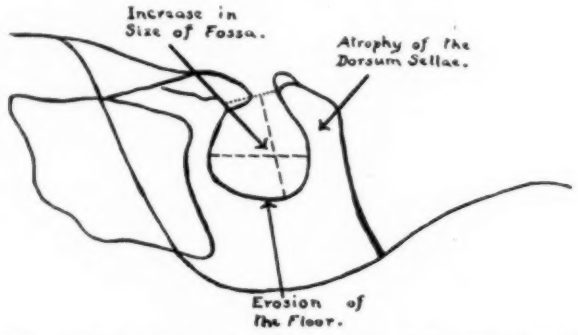

Fig. 7.—The cardinal changes in deformations of the sella turcica. Drawing indicates the manner in which the pituitary fossa is measured.

minor and infrequent changes occur that at times may aid in the more accurate localization of a suspected lesion, it is on the recognition and proper evaluation of the cardinal changes that chief reliance must be placed in the interpretation of roentgenograms of the sella turcica.

Figure 7 illustrates the manner in which the measurements of the pituitary fossa are made. The horizontal broken line represents the greatest anteroposterior measurement of the fossa. To obtain the depth, represented by the vertical line, the position of the diaphragma sellae must be determined. This passes from the tuberculum sellae backward to the top of the dorsum sellae, shown by the dotted line. A line perpendicular to the diaphragma sellae is dropped to the greatest depth of the fossa. This represents the depth measurement. This means of determining the size of the pituitary fossa differs, of course, from the various methods employed elsewhere, but since the measurements are of only comparative value, the method used is of little

importance provided one always makes use of the same method. Furthermore, minor variations in measurements are of no importance, as changes in size must be definite and appreciable in order to be of clinical value.

Measured in the manner described, 10 mm. in the anteroposterior direction and 8 mm. in depth are considered average measurements for the adult sella. The fossa is not considered enlarged unless the measurements exceed 12 mm. in the anteroposterior direction and 10 mm. in depth. No significance is attached to top normal measurements unless accompanied by other definite evidences of disease either in the sella or elsewhere in the skull. Reductions in the size of the fossa are apparently without significance. Various investigators have found no definite relationship existing between the size of the head and the size of the fossa. Likewise, sex is of no importance. As has been mentioned, the fossa is proportionately smaller in children.

TABLE 1.—*Classification of Lesions Producing Deformity of the Sella Turcica*

1. Intrasellar lesions	Direct or localized pressure
2. Extrasellar lesions	Direct or localized pressure
a. Suprasellar	Direct or localized pressure
b. Parasellar	Direct or localized pressure
c. Metasellar	Indirect or transmitted pressure (increased intracranial pressure)
3. Lesions of the sphenoid bone	

Lesions responsible for alterations in the sella turcica may be classified according to the characteristics of the changes produced (table 1). The changes are dependent on the location of the lesion. It is usually possible to distinguish between the sellar changes resulting from lesions located within the pituitary fossa and those occurring outside of the fossa. Thus, there are the two main groups of intrasellar and extrasellar lesions. The extrasellar group can be divided further into three divisions, dependent on the more accurate localization of the lesion. Lesions occurring just above the sella are designated as suprasellar, those located alongside of the sella in the middle cranial fossa have been called by Mayer [4] parasellar, while lesions occurring beyond or at a distance from the sella, we have termed metasellar lesions. In addition to the two main groups of intrasellar and extrasellar, there remains still a third group comprising alterations due to diseases of the sphenoid bone itself. The latter group will not be dealt with in this paper.

4. Mayer, Ernest G.: Roentgenographic Examination of the Base of the Cranium in the Presence of Basal Tumors, Radiology **10**:319, 1928.

The deformities of the sella turcica resulting from intracranial lesions are produced in one of two ways: either by direct or localized pressure by the lesion itself on the various bony structures of the sella, or by indirect or transmitted pressure by way of a dilated third ventricle. The manner in which the various lesions produce their effect on the sella turcica is indicated in table 1. This, however, is not a hard and fast rule, since in certain cases one or another of the types of pressure may be operative. For instance, in a parasellar lesion there may be direct pressure by the lesion on the sella, or the pressure may be transmitted by way of the internal carotid artery. Likewise, an angle tumor, ordinarily classified as a metasellar lesion, if properly located, may cause direct pressure on the posterior aspect of the dorsum sellae, pushing the dorsum and posterior clinoid processes forward, as has been described by Schüller and by Mayer. In other cases, both types of pressure may be responsible for the sellar deformity.

In those metasellar lesions accompanied by increased intracranial pressure, I have thought that the most important factor responsible for alterations in the sella turcica is direct pressure on the sella by a dilated third ventricle. In this type of deformity the factor of prime importance is the location of the lesion. Its histologic structure or size is of little significance. Thus, a small tumor obstructing the aqueduct of Sylvius will, as a rule, produce greater deformity of the sella turcica than will a large tumor not in relation to the ventricular system. It must be conceded, however, that deformity of the sella turcica may occur in association with lesions that do not obstruct the ventricular system. Here the changes, no doubt, are due simply to the general increase in intracranial pressure. The dorsum sellae, which is usually involved in such cases, projecting unprotected up into the cranial cavity, is peculiarly liable to be affected by abnormal increases in intracranial pressure.

The most characteristic and the most readily recognized deformity of the sella turcica is that seen in intrasellar lesions (fig. 8). Here the characteristic changes are a general uniform enlargement of the pituitary fossa, an erosion of the floor, with or without encroachment on the sphenoid sinus, and atrophy of the dorsum sellae. The appearance of the dorsum in such cases is of special importance. The erosion of this structure occurs on its anterior aspect, while at the same time, the dorsum is displaced backward and upward. The posterior clinoid processes are often preserved. The deepening of the fossa, as a result of erosion of the floor, gives the dorsum an appearance of having been elongated. This picture as described is almost pathognomonic for a pituitary tumor, usually an adenoma. In figure 8, there will be noted a pointing and upward displacement of one of the anterior clinoid

processes, indicating a greater growth of the tumor in that direction. Often, it will be found that the clinical symptoms are predominant on the side of the deformed anterior clinoid process. To determine which of the two processes is deformed, one must rely on the stereoscopic films.

Unquestionably, the most common type of deformity of the sella turcica is that seen in metasellar lesions (fig. 9), because these comprise

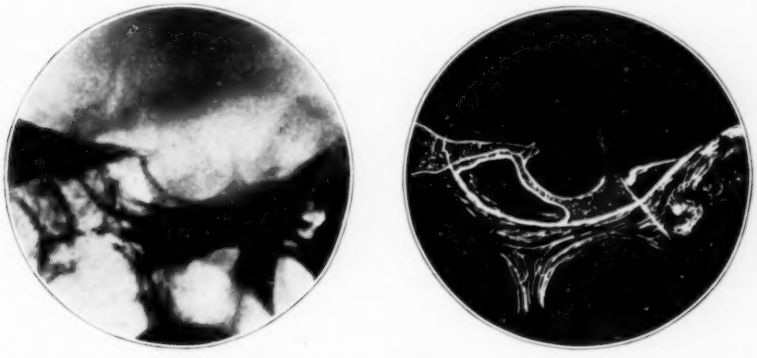

Fig. 8.—The characteristic deformation of the sella turcica as the result of an intrasellar lesion. Left, original roentgenogram; right, drawing made from the roentgenogram.

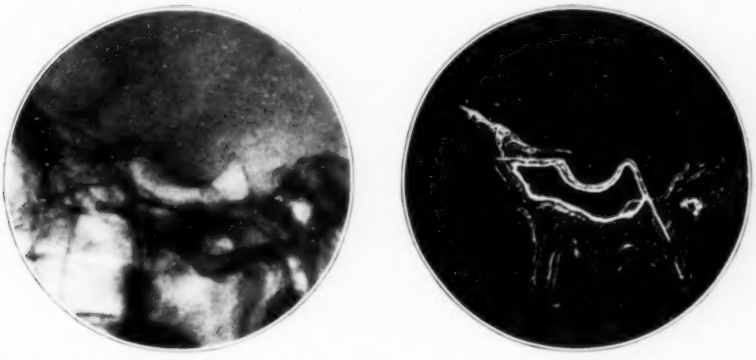

Fig. 9.—The characteristic deformation of the sella turcica as the result of a metasellar lesion.

the largest group of intracranial lesions capable of producing sellar changes. Since these lesions produce their effect indirectly by transmitted pressure through an enlarged third ventricle or by a general increase in intracranial pressure, the first structure to be involved is the dorsum sellae. The pressure, being directed from above, first causes a disappearance of the posterior clinoid processes. The dorsum is then eroded, until eventually it may disappear entirely. There is an accom-

panying enlargement of the pituitary fossa resulting from the atrophy of the dorsum, the enlargement being chiefly, and at times only, in the anteroposterior diameter. There may be no erosion of the floor of the pituitary fossa and no encroachment on the sphenoid sinus. The anterior clinoid processes usually remain undisturbed.

The two types of deformity already described comprise by far the largest number of lesions that may alter the sella turcica. In addition,

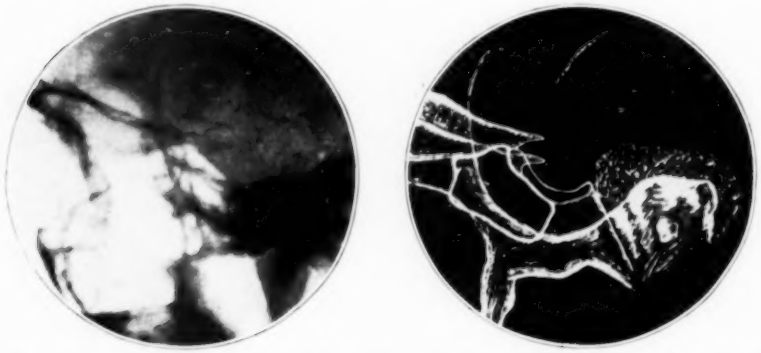

Fig. 10.—The characteristic deformation of the sella turcica as the result of a suprasellar lesion. Note the calcification in the tumor above the sella.

Fig. 11.—The characteristic deformation of the sella turcica as the result of a parasellar lesion.

they also produce the most characteristic deformities. The remaining lesions are recognized with much more difficulty and uncertainty. In figure 10 is seen the deformity of a suprasellar tumor. Here, there is usually a definite enlargement of the pituitary fossa involving both the anteroposterior and depth measurements. Particularly is the entrance of the pituitary fossa enlarged. The sphenoid sinus is usually but not invariably encroached on. The dorsum sellae undergoes marked atrophy,

often being entirely absent. Frequently, the anterior clinoid processes are eroded, causing them to be pointed as shown in figure 10. One of the characteristic and most helpful features of suprasellar tumors is that many of them present irregular areas of calcification (fig. 10). In fact, the roentgenologic diagnosis is usually made possible by the finding of such calcification.

The most infrequent and the most difficult to recognize from evidence presented by the sella turcica is the so-called parasellar lesion, that is, one lying alongside of the sella in the middle cranial fossa. Figure 11 is an example of such a case. There will be noted a double floor to the pituitary fossa, showing that it has been eroded more on one side than the other. The dorsum sellae is quite indistinct, suggesting atrophy. Behind the dorsum is the ossified dura overlying the clivus. There is

Fig. 12.—Same case as in figure 11. Normal appearance on the left side and unilateral deformation of the sella on the right, due to a lesion in the right middle cranial fossa.

a distinct difference in the anterior clinoid processes on the two sides. One is normal in appearance, while the other is pointed and pushed upward. It is evident that alterations have involved but one side of the sella, but it is impossible from the flat film to determine which side is affected. Consulting the stereoscopic films of each side, one of each pair being shown in figure 12, it will be noted that on the left side the pituitary fossa shows no enlargement; the anterior clinoid process and dorsum sellae are normal in contour. Contrast this with the appearance on the right side. Here, the fossa is definitely enlarged with considerable erosion of the floor, the dorsum sellae is absent and the anterior clinoid process is deformed; there is some calcification of the diaphragma sellae and of the dura overlying the clivus. There is also some abnormal calcification present. These changes would indicate an alteration involving only the right side of the sella turcica. At opera-

tion, there was found an endothelioma in the right middle cranial fossa just lateral to the internal carotid artery. Pressure from the tumor, transmitted by way of the artery, was evidently responsible for changes found in the sella. Unilateral alteration in the sella turcica, therefore, should lead one to suspect a parasellar lesion.

The cases cited are fairly typical examples of the various lesions indicated in the classification. There are, however, many atypical cases

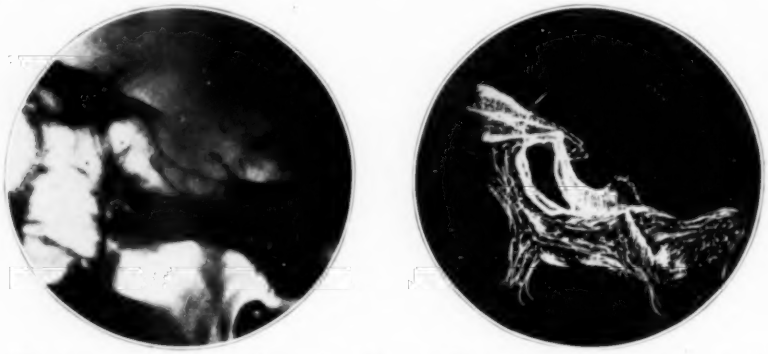

Fig. 13.—An atypical deformation of the sella turcica due to a primary pituitary tumor with a large suprasellar extension.

Fig. 14.—A pituitary tumor simulating the deformity of a metasellar lesion. The diagnosis of pituitary tumor was suggested on the basis of the double floor of the fossa.

in which the changes partake of more than one type of lesion. The picture in such cases is very confusing. In figure 13 there is seen a definite deformity of the sella consisting of an enlargement of the fossa and atrophy of the dorsum sellae. There will be noted a double floor to the fossa indicating a greater erosion on one side than on the other. Because of this observation a diagnosis of a pituitary tumor

was made. A subsequent encephalogram indicated rather conclusively a suprasellar tumor. At operation, a large suprasellar tumor was found. The patient subsequently died, and at the postmortem examination it was shown that the suprasellar tumor was merely a suprasellar extension of a primary pituitary tumor.

In figure 14 is to be seen a deformity suggestive of a metasellar lesion in that there is atrophy of the dorsum sellae from above, and the pituitary fossa has been enlarged chiefly in the anteroposterior direction. There will be noted, however, a double floor to the fossa. This is an observation of considerable importance, and while it may

TABLE 2.—*Analysis of One Thousand Roentgenologic Examinations of the Head*

	Number	Per Cent
Normal sella turcica	886	88.6
Abnormal sella turcica	114	11.4
Total	1,000	

TABLE 3.—*Deformation of the Sella Turcica in One Hundred Verified Cases of Brain Tumor*

	Number	Per Cent
Abnormal sella turcica	61	..
Normal sella turcica	39	..
Total	100	
PATIENTS UNDER 12 YEARS OF AGE		
Abnormal sella turcica	4	26
Normal sella turcica	11	74
Total	15	
PATIENTS OVER 12 YEARS OF AGE		
Abnormal sella turcica	57	67
Normal sella turcica	28	33
Total	85	

be found in metasellar lesions, I am of the opinion that it is much more commonly encountered in tumors in or about the sella, especially intrasellar tumors. Because of the double floor in this case, a diagnosis of a pituitary tumor was made. This was subsequently confirmed at operation.

While alterations in the sella turcica are exceedingly valuable in detecting the presence of intracranial disease, it is only in the exceptional case that one is justified in venturing a diagnosis from the appearance of the sella turcica alone. The changes found in the pituitary tumor are the only ones that are at all pathognomonic. It is essential, in addition to the sellar deformity, that the roentgenologic changes found elsewhere in the skull and the clinical manifestations be taken into consideration, as it is only after a thorough correlation of such data

that one is justified in attempting to evaluate and interpret the changes found in the sella turcica. This is a point that cannot be too strongly emphasized.

In an attempt to determine the incidence of deformations of the sella turcica, an analysis was made of 1,000 roentgenologic examinations of the head, with the result shown in table 2. It will be seen that alterations in the sella were found in approximately 10 per cent of the patients examined. This rather high incidence was somewhat surprising, but is due, no doubt, to the active neurologic and neurosurgical services of the University Hospital.

By way of contrast, 100 unselected but verified cases of tumor of the brain were analyzed to determine the incidence of sellar deformity in this group. The result is shown in table 3. It was found that 61 per cent of the cases showed a deformity of the sella turcica. This is in marked contrast to the 10 per cent found in the group of table 2. Dividing the group of 100 into persons younger that 12 years of age and those over 12, it will be noted that only 25 per cent of the former group showed sellar changes; in adults the incidence was 67 per cent. From these analyses it is evident that deformations of the sella turcica occur sufficiently often to make them a valuable aid in the detection of intracranial disease.

CONCLUSIONS

1. Alterations in the structure of the sella turcica, as revealed by the roentgen ray, are, in a high percentage of cases, indicative of intracranial disease.

2. Lesions capable of producing changes in the sella turcica may be classified according to the characteristics of the changes produced, these changes being dependent on the location of the lesion.

3. Deformations of the sella are, in themselves, rarely diagnostic, but when correlated with other roentgenologic observations in the skull, as well as with the clinical manifestations, they offer valuable aid in the localization of suspected intracranial lesions.

ABSTRACT OF DISCUSSION

DR. W. G. SPILLER: In a recent conversation with Dr. H. K. Pancoast concerning some cases of brain tumor in which the roentgenograms suggested moderate atrophy of the dorsum sellae he stated that this appearance must be carefully interpreted, because it is not absolute proof of pressure of the third ventricle or even of brain tumor. The appearance of early atrophy from these causes may be simulated by the rarefaction of the dorsum that results from enlarging blood spaces in this portion of the base occurring in middle life or later. According to Dr. Batson, the dorsum is a vascular rather than a marrow cancellous bone, the blood channels being intimately connected with the basilar sinus. Their enlargement with advancing years may produce an appearance closely simulating the early atrophy of the dorsum from pressure of the third ventricle.

DR. KARL KORNBLUM: My answer to Dr. Spiller is that he is perfectly correct in saying that occasionally one sees erosion of the dorsum sellae and disappearance of the posterior clinoid processes in the absence of a lesion within the cranial cavity. I think that many cases of this kind fall in the group in which there is physiologic atrophy, as explained in my presentation. Also in childhood, during periods of temporary increase in intracranial pressure, the dorsum sellae may become atrophic. Such changes are permanent because, of course, the dorsum does not regenerate. That atrophy of the dorsum is not an absolute proof of an intracranial pathologic condition is evident. One cannot base a diagnosis on the absence of the dorsum sellae alone; there must be other changes as well. Dr. Grant has brought up an important point, namely, that the diagnosis cannot be made from the appearance of the sella turcica alone. The only lesion in which the changes in the sella turcica are at all characteristic is the pituitary adenoma. In a lesion of the posterior fossa one frequently finds other changes in the roentgenograms that immediately rule out a suprasellar or pituitary tumor. I think that one must take into account the history, the clinical manifestations and the other roentgenologic changes produced in the skull before attempting to interpret the changes found in the sella turcica.

NEURITIS FROM ARSENIC AND LEAD

THE SIGNIFICANCE OF CHEMICAL STUDIES IN DIAGNOSIS *

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It has long been known that arsenic is eliminated in part in the urine. During the epidemic of multiple neuritis in Manchester, England, in 1900, Reynolds, Mann and others found that the beer used in the community became contaminated with arsenic in manufacture, and that these "beer-drinking" patients were excreting arsenic in the urine. They concluded that arsenic, rather than alcohol, was responsible for the so-called alcoholic neuritis that had long been present about Manchester. Mann also found that the hair, scales from the feet and hands, and nails of these patients contained arsenic.

We are certain that the excreta and the skin and its appendages must have been examined for arsenic in forensic medicine, and also in isolated cases in clinical practice when suspicions of its presence arose. Nevertheless, we have not found any reference to the use of chemical methods as a routine procedure in determining the part that arsenic may play in the causation of multiple neuritis.

Our first attempt to use these methods for diagnostic purposes was in 1922, when, at the suggestion of Dr. J. H. Stokes, a chemical examination of a twenty-four hour specimen of urine revealed 50 mg. of arsenic. The patient had secondary anemia, and pigmentation and keratosis developed during treatment with solution of potassium arsenite.

Our interest in this study has developed tardily, since about 1926. The pursuit of such a study is subject to no little difficulty. The majority of our patients are from remote parts. Therefore, it is the exception for patients to be willing to remain at the clinic long enough for a sufficient number of consecutive samples of urine to be collected to make such a study of scientific value. Admitting this deficiency, we believe that our data warrant some confidence in their clinical value,

* Submitted for publication, June 2, 1931.

* From the Section on Neurology and the Section on Biochemistry, the Mayo Clinic.

* Read at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 27, 1931.

TABLE 1.—*Multiple Neuritis Following Arsenical Medication*

Case	Age (Yrs.) and Sex	Date of Chemical Determination	Arsenic, Mg. in Each 1,000 Cc. of Urine	Lead, Mg. in Each 1,000 Cc. of Urine	Medication	Severity of Multiple Neuritis	Clinical Notes
1	29 M	8/21/29 8/24/29 8/27/29	0.6 None None	0.15 None	Arsphenamine	Mild	On Aug. 24, 1929, 0.05 mg. of arsenic in 1.8 Gm. of hair; for two years, tingling in feet; pain in arms and legs; vibration sense reduced in feet; last arsphenamine given one year before registration
2	51 M	12/22/26	4.0	None	Acetarsone	Mild	Amebiasis; in April and May, 1926, 24 tablets and acetarsone; in September, 1926, 24 tablets; paresthesia of hands and feet; reduced achilles reflex; vibration sense markedly reduced
3	37 M	6/25/29	0.62	None	Neoarsphenamine	Mild	Paresthesia of feet; achilles reflex markedly reduced; pain, touch and temperature sensibility much reduced in legs
4	63 M	4/ 6/27 4/ 7/27 5/26/27 6/20/27 8/25/27 9/27/29 9/28/29 10/18/29 7/ 1/30	None 26.6 16.3 20.0 15.0 0.75 0.62	None	Acetarsone	Mild	Amebiasis; on March 16, 1927, acetarsone (0.25 Gm.), 15 doses; on April 1, 1927, acetarsone, same dosage; about May 1, 1927, paresthesia and numbness in the extremities; on Sept. 9, 1929, recurrence of dysentery; emetine and treparsol* (0.25 Gm.), 12 doses; on Sept. 23, 1929, same amount, 8 doses
5	40 M	4/ 4/28	1.75	0.14	Arsphenamine	Mild	In January, 1928, 6 doses of arsphenamine followed by paresthesia and ataxia; some pain in legs
6	45 M	3/ 9/27 3/31/28	16.0 None	None	Neoarsphenamine	Mild	Last treatment in January, 1927; numbness, tingling and swelling of toes and fingers
7	51 F	5/31/28	1.25	None	Neoarsphenamine	Mild	Treatment since June, 1927; paresthesia; achilles reflex lost; pressure pain increased
8	50 F	12/19/28 12/24/28	None None	None None	Intravenous, substance not stated	Mild	Vesicular eruption following 5 injections in September, 1928; pigmentation, arsenical type, following recovery from eruption; pain in legs; achilles reflex lost
9	59 M	6/18/29 6/24/29 7/17/29	0.06 None	0.08 0.06 None	Sulpharsphenamine	Mild	On March 11, 1928, syphilitic aortitis; blood test 4+; patient was a painter; in July, 1928, numbness, pain and tenderness of feet; September, numbness of hands; both achilles reflexes moderately reduced; 8 doses; last treatment in May, 1928; further arsenical treatment at home
10	48 M	10/28/29 5/26/30	0.62 None	None None	Neoarsphenamine	Moderate	Treatment in July, 1929; paresthesia and numbness on Sept. 1, 1929; achilles reflex lost; vibration markedly reduced; pressure tenderness
11	37 M	11/ 9/27	0.5	None	Neoarsphenamine	Moderate	Treatment in September, 1926; in November, 1926, numbness; tingling, and pain in feet; moderate weakness in legs; achilles reflex absent; pressure tenderness
12	54 M	8/13/29 8/15/29	None 1.1	None None	Arsphenamine	Moderate	Treatment in March, 1929; paresthesia and numbness in May, 1929; achilles reflex absent; vibration sense reduced; pressure pain increased
13	37 F	2/15/29	3.78	0.05	Sodium cacodylate	Severe	From October, 1928, to February, 1929, 48 injections; paresthesia began in October, progressive; marked weakness; ataxia; knee and achilles reflexes lost; vibration sense lost in legs; pressure pain increased

* A proprietary preparation, a methenamine derivative of meta-amino-para-oxyphenylarsenic acid (this has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association).

and we even entertain the hope that future study may widen our experience and provide data that are now lacking. The four tables include forty cases, five of which are reported in more detail in the text.

The greatest hindrance of all to progress in this problem is lack of knowledge of the distribution of arsenic, and even though its presence in the body is known, prevention of its further entrance fails from lack of acquaintance with its source. Of course, we are aware of the wide distribution of arsenic in nature, and that it is an inevitable contaminant of many useful chemicals and materials used in the arts and in industry. As a constituent of insecticides it contaminates our food; in pipes and conduits it reaches our water supply, and by other inconstant, accidental and intentional methods it gains access to the human organism. Confronted with an individual sufferer, in a complicated and irresponsible society, the detection and control of intake of arsenic are perhaps beyond us at present.

Not only do individual persons show great variation in their clinical reaction to arsenic, but there exists much individual variation in the biochemical affinity of different tissues for this element. Even in so small a group as we present, the skin, mucous membrane, vessels, nerves, muscles and liver, each has shown selective affinity for the metal. We have no knowledge of the factors that determine these variations.

From our data we must consider that elimination of arsenic in any amount is of clinical significance, and especially so if symptoms exist that may be consistently attributed to the element. In other words, the amount of arsenic eliminated furnishes no reliable guide to the physical injury that is wrought by it. It is the retained arsenic, of course, that does the harm. Thus far there is no known method of determining the amount within the body; neither is the type of protoplasm known with which arsenic most readily unites.

Considerable study has been given to the behavior of organic preparations of arsenic within the body (Meyers and his co-workers), and certain general conceptions, or averages, are known in relation to the persons studied. Such work might also be done with the inorganic salts and preparations. A few of our cases actually illustrate such behavior. Any general rule is of little value, however, if there exists a considerable proportion of persons who are exceptions in their biochemical reactions. In fact, we are inclined to look on the cases here reported as a list of exceptions. Even these exceptions are not readily classified as such, each behaving according to an individual pattern.

We have three interesting observations to offer concerning arsenic and lead which furnish a foundation for the statements just made. Case 19 is that of a woman who is housekeeper for her brother and has lived in his present house for several years. In this environment the clinical syndrome developed that is here reported. Her brother was

unaffected, yet 1,000 cc. of his urine contained 15 mg. of arsenic in a sample tested in the course of their first visit to the clinic. The man in case 24 came with pronounced neuritis, and was excreting greatly varying amounts, from none to 10 mg. for each 1,000 cc. of urine in a series of five tests. His friend, living in the same household, who accompanied

TABLE 2.—*Multiple Neuritis in Which Source of Lead and Arsenic Is Unknown*

Case	Age (Yrs.) and Sex	Date of Chemical Determination	Arsenic, Mg. in Each 1,000 Cc. of Urine	Lead, Mg. in Each 1,000 Cc. of Urine	Pigmentation	Severity of Multiple Neuritis	Clinical Notes
14	49 M	11/ 1/29 11/ 3/29	7.5 7.5	None	Absent	Mild	Numbness in toes began in March, 1929; achilles reflex lost; vibration and joint sense reduced; pressure pain increased
15	50 F	12/31/29 1/ 6/30	1.25 1.8	0.04	Absent	Mild	Pain in feet in September, 1929; pressure pain slightly increased
16	32 M	3/19/28 3/20/28 3/21/28	2.5 None 2.5	None	Absent	Mild	Numbness in feet and hands for two weeks; reduction of vibration sense in feet
17	37 M	10/15/27	2.46	None	Absent	Mild	Paresthesia and pain in legs and hands since June, 1927; pressure pain somewhat increased
18	39, M	.....	....	....	Present	Moderate	See case report
19	59, F	.....	....	....	Present	Moderate	See case report
20	31 M	1/ 3/30 11/11/30	0.61 None	0.16 None	Absent	Severe	In August, September and October, vomiting for from five to eight days; weakness and numbness began in legs in September, and in hands later; ataxia in arms and reflexes in legs lost; vibration sense reduced; joint sense lost
21	32 F	2/10/27 2/11/27 2/28/27	2.14 2.3 13.0	None	Absent	Severe	Became pregnant in June, 1926; vomited for seven weeks, beginning in August; in third week of vomiting, numbness and weakness of legs; some pain; miscarriage in November, 1926; knee reflexes much reduced; achilles reflexes absent; vibration and joint sense much reduced
22	61 M	7/ 2/27 7/ 7/27 7/14/27 7/20/27	7.0 None 2.4 None	None	Absent	Severe	Since 1924, numbness and weakness progressive; knee and achilles reflexes lost; vibration sense lost; joint sense reduced
23	66 M	3/21/27 3/29/27 4/ 1/27 4/ 4/27 7/ 1/27	12.5 10.0 None None None	None	Absent	Severe	In August, 1926, nausea and vomiting for ten days; in September, 1926, hypesthesia and then numbness in legs, later in fingers; vibration sense much reduced; pressure pain increased; improving
24	35 M	2/17/30 2/20/30 2/22/30 2/25/30 2/28/30	2.5 None None 10.0 1.9	None	Absent	Severe	See case report
25	43 M	4/ 6/27	33.3	0.23	Present	Severe	Painter; for two years paresthesia, hypesthesia and tenderness of legs and hands; moderate weakness; pigmentation; keratosis of soles and palms; no stippling of erythrocytes; achilles reflex lost; pressure pain increased
26	46 F	5/16/30 11/ 5/30 11/ 7/30 11/11/30	1.92 5.0 1.25 1.85	None None 0.12 None	Present	Severe	See case report
27	40 M	11/13/30 1/ 6/31	1.27 None	None None	Present	Severe	See case report

him, excreted in the urine 34 and 23 mg. to the liter on two successive examinations. The friend was in normal health. The man in case 18 and his wife were excreting similar amounts of lead, yet neuritis affected the man only. From such experiences one must presume some decidedly specific reaction of the afflicted person, or that the metals must be considered of no consequence.

Five of the patients with multiple neuritis had pigmentation of the skin. The character and distribution of this pigmentation are such that objectively they suggest conditions of arsenical origin.

The patient in case 25 had pronounced neuritis, and excreted 33.3 mg. of arsenic in 1,000 cc. of urine. In cases 19, 26 and 27, the output of arsenic was variable, averaging 2 mg. in each 1,000 cc. of urine. In case 6, the pigmentation followed medication with arsenic, but the urine was free from arsenic at the time of the patient's examination.

The skin may exhibit definite selectivity for arsenic, and many patients have cutaneous changes only. Considerable quantities of arsenic may be stored in the skin, hair and nails, from which it may be recovered chemically, and Osborne developed a stain by which to identify it microscopically in the skin. The amount of arsenic excreted in the urine by patients with objectively characteristic cutaneous lesions serves as further evidence of the significance of similar amounts of arsenic in the urine of patients who have neuritis only.

The initial symptoms of five patients of the group were episodic attacks of protracted nausea and vomiting. In two cases the neuritis began during the second episode. These gastro-intestinal symptoms afforded additional presumptive evidence of the ingestion of arsenic in amounts exceeding physiologic tolerance.

In ten cases of the twenty-seven in which multiple neuritis was present, lead was found associated with arsenic. Of these ten cases, in seven the source of the arsenic and of the lead was unknown, whereas in three the arsenic was taken medicinally. The combination of arsenic and lead does not appear to alter the character or severity of the neuritis in any way. The presence of lead in the cases in which the source was unknown offers a presumption that it was introduced in combination with arsenic as arsenate of lead, which is often used in husbandry as an insecticide. However, we had no facts to support such a contention. In this respect a case of interest is offered. The first chemical examination of a fifteen hour sample of urine (volume not given) of a patient suffering with neuritis of two and a half years' duration revealed 16 mg. of arsenic and no lead. Eighteen tests of the urine for arsenic and lead were made during the ensuing nine months. Twelve of the tests gave evidence of lead in amounts varying from 0.38 to 0.63 mg. in the samples tested, and six gave no evidence of lead. The patient's wife had 0.59 mg. of lead in 4,000 cc. of urine on July 28,

1927, namely, about five months after we first found lead in the patient's urine. Evidently both were getting the lead from a common source. Their drinking water contained 0.07 mg. of lead in a gallon (4 liters). It is questionable whether such a diluted source can be considered the sole supply. In this case one may speculate on the effect of the arsenic in producing the neuritis. However, we assumed that the neuritis was due to the lead. The patient recovered steadily under treatment directed against lead.

TABLE 3.—*Multiple Neuritis Associated with Excretion of Lead But Not of Arsenic*

Case	Age, Yrs.	Sex	Date of Chemical Determination	Lead, Mg. in Each 1,000 Cc. of Urine	Severity of Multiple Neuritis	Clinical Notes
28	57	M	4/15/29	0.15	Mild	For two years paresthesia and numbness; tenderness of soles; slight ataxia; some fibrillary twitching in hands; achilles reflex lost; vibration sense much reduced; slight distal anesthesia
29	31	M	8/26/29 8/29/29 9/3/29 9/13/29	0.44 0.45 0.02 None	Moderate	Fibrillary twitching in hands; throat cultures negative; for three months, peripheral paresthesia, pain, anesthesia, weakness and atrophy of moderate degree; pressure pain increased
30	27	F	5/16/29	0.46	Severe	In January, 1925, weakness and pain in arms and legs; in March, 1925, three injections of iron and arsenic; in 1928, 11 injections of sodium cacodylate with toxic symptoms; intermittent course; reflexes of arms and legs lost; weakness marked
31	28	F	1/12/29	0.17	Severe	For three months, paresthesia, pain and numbness of hands and feet; marked weakness of legs; reflexes of arms and legs lost; joint vibration and superficial sensibility much reduced in legs
32	36	M	11/15/27 11/17/27 11/21/27	0.15 0.08 None	Severe	Cold two months before registration; six weeks before registration, tingling and numbness of hands and feet; weakness; ataxia; reflexes of arms and legs lost; vibratory and joint sense much impaired; moderate anesthesia
33	38	F	12/21/28 12/26/28	0.53 None	Severe	In August, 1928, abdominal pain; jaundice; on November 15, cholecystectomy with removal of stones; about November 23, tingling and numbness; weakness; reflexes absent; vibratory and joint sense lost in legs; anesthesia marked in legs and hands

Lead is said to be retained much longer than arsenic, and if taken in a form such as lead arsenate, the two elements become dissociated in the body and are subject to independent excretion.

In speculating as to the significance of the presence of arsenic in the urine, many factors must be considered. These are: (1) the type of arsenic introduced; (2) the length of time over which it is taken into the body, and (3) the susceptibility of the patient. Such factors apply also in the instance of lead, but the absolute amounts of lead are much less than those of arsenic.

As has been said, the amounts of these elements excreted bear no particular relationship to the clinical condition. Large amounts of arsenic in the urine indicate only that the intake has been recent, and the patient

may exhibit no indication of arsenical poisoning, whereas the absence of arsenic from the urine and its presence in the hair may be indicative of long storage of this substance, with its possible untoward effect. Similarly, in the case of lead, which is intermittent in its excretion, its complete absence may indicate only that metabolism has resulted in

TABLE 4.—*Multiple Neuritis Without Excretion of Arsenic or Lead*

Case	Age, Yrs.	Sex	Date of Chemical Determination	Severity of Multiple Neuritis	Clinical Notes
34	48	M	12/ 6/29	Mild	In September, 1928, numbness and tingling in feet; slowly progressive and constant; some weakness; slight ataxia; slight reduction of vibration and pain sense; reflexes normal
35	61	M	6/19/29	Mild	Penile sore in June, 1928; 6 doses of arsphenamine; sodium cacodylate, 4 doses in January, 1929; 5 negative Wassermann tests; on July 1, 1928, onset of numbness; pain and tenderness of hands and feet; knee reflexes reduced; achilles reflex much reduced
36	51	M	9/16/29	Moderate	Gastro-enterostomy for duodenal ulcer in 1929, with good result; in 1927, some swelling of calves and uncertain gait; recovered in three or four weeks; about Sept. 1, 1929, paresthesia in legs and fingers; moderate ataxia and weakness of legs; reflexes of arms normal; knee and achilles reflexes absent; vibration and joint sense normal; pain, temperature and touch sensibility reduced in legs; tonsillectomy; on Dec. 18, 1929, much improved
37	58	M	11/ 7/27 11/10/27	Moderate	History of syphilitic infection eight years before admission; in June, 1927, 6 injections of arsphenamine; soon after sixth injection, tingling and pain in legs and hands; spinal fluid contained 17 cells; weakness in legs; reduction of arm and knee reflexes; achilles reflexes absent; vibration sense lost in legs; joint sense reduced; pressure tenderness in legs
38	54	M	11/25/27	Moderate	Quinsy in August, 1927; in October, 1927, tingling, numbness, pain and weakness in legs and hands; tonsillectomy; throat culture negative; reflexes in arms and knees greatly reduced; achilles reflex absent; vibration and joint sense reduced in legs
39	32	M	11/18/27	Moderate	On Aug. 24, 1927, sore throat; diphtheria bacilli in culture; antitoxin; tonsillectomy, October 8; about October 15, numbness, weakness and ataxia of feet and hands; swallowing with difficulty; blurred vision; moderate weakness; reflexes lost; vibration sense lost; moderate distal anesthesia; pressure pain increased; postdiphtheritic neuritis
40	54	M	11/29/29	Moderate	Two months before registration, paresthesia and numbness of both feet and hands; later, weakness of legs; reflexes of arms and legs absent; vibration sense lost in feet; pain sense slightly reduced; sciatic and peroneal nerves sensitive

storage of the entire amount of the introduced metal. In order to mobilize the lead from the storage depots it may be necessary to produce increased calcium metabolism. The excretion of lead, under these conditions, may be indicative of preceding lead poisoning.

Of course, no one can contend that the presence of arsenic or of lead in the urine of a patient with multiple neuritis establishes positive proof of a causal relation of the metal to the neuritis. In fact, with the possible exception of leprosy, there is no means of positive identification of the etiologic factor. The most substantial etiologic influence, in

forms of neuritis of common occurrence, is found in diphtheritic neuritis, in which the bacterial cultures are definite and the distribution of the associated palsy is characteristic. To treat a patient with multiple neuritis, which is presumed but not known to be due to the ingestion of arsenic or lead, without chemical studies which might readily reveal the probable cause may prolong morbidity and prevent consistent and successful treatment.

Arsenic has been determined by the electrolytic Gutzuiet procedure, as described by one of us (Dr. Osterberg), and lead by the Fairhall technic.

The neuritis has been classified as severe, moderate or mild, based largely on the degree of muscular weakness. This classification is arbitrary, and has only a relative value, for the purposes of tabulation. It is obvious that no definite uniformity of signs occurs, and for this discussion we trust that the interpretation of the signs and symptoms will be accepted.

REPORT OF CASES

CASE 19.—A woman, aged 59, came to the clinic on April 14, 1927. The family history was without significance. Since the onset of menstruation she had had profuse hemorrhages, for which hysterectomy was performed in 1915. Since early adult life she had had secondary anemia, for which iron and arsenic was given hypodermically in 1911. Intermittent courses of such medication, over periods of two months, were given five times yearly for the next five years. In 1921, weakness in the legs was first noted. This had been continuous since and also somewhat progressive. In October, 1925, pain, numbness and tingling had appeared in the left foot and in the hands. Associated with these symptoms she had had unsteadiness of gait, sensitiveness of the feet, a subjective feeling of cold in the feet and shooting pain in the legs. Since 1927, she had had purpuric spots on the legs and arms for periods of four or five days, occurring intermittently up to the time of her registration. Since July, 1929, there had been moderate arthritis in the shoulders, elbows and hands, with some residual stiffness of the fingers.

General examination indicated a normal condition. Urinalysis, blood count, Wassermann test of the blood and analysis of gastric content gave negative results. The systolic blood pressure in millimeters of mercury was 130; the diastolic, 70. There was mild secondary anemia. The cranial nerves were normal. The legs were weak, especially the anterior and posterior tibial muscles, the peroneal muscles and the flexors of the toes. The grip of the hands was somewhat reduced. The brachial reflexes were normal, the knee reflexes reduced, the achilles reflexes absent, and the vibratory sense and pain, tactile and temperature sensibility moderately reduced. Pressure pain was increased in the legs. On exposure to cold the vasomotor response caused local pallor. In May, 1930, the nails appeared rough and were curved. There was also some atrophy of the thenar muscles, and there was ulnar deflection of the fingers. In the skin there was slight pigmentation of the arsenical type. These features were readily identified as those of multiple neuritis, and twenty-four hour specimens of urine were collected to be tested for lead and arsenic. On April 18, 19, 27 and 29, 1927, 1,000 cc. of urine contained, respectively, 4.1, 11.3, 3.0 and 6.0 mg. of arsenic. There was no evidence of lead. In 500 mg. of the patient's hair there was 0.187 mg. of arsenic.

The patient was accompanied by her brother, a man of about her age, who lived in the same household. A twenty-four hour sample of his urine contained 15 mg. of arsenic. As the urine of sister and brother contained arsenic, it was thought that the water supply at their home should be investigated. They had lived in the same house for forty-eight years, and about seventeen years before their registration the plumbing had been installed. Water from the faucet from which the drinking water was obtained was examined on April 19 and April 29, 1927, and 2.5 and 2.0 mg. of arsenic for each liter was found. There was no evidence of lead. Extensive alteration of the plumbing was instituted, and on many subsequent tests only traces of arsenic could be found.

The patient made subsequent visits to the clinic, and on May 14, 1928, and May 1, May 3 and May 16, 1930, respectively, 1.0, 0.6, 0.61 and 0.61 mg. of arsenic was found in 1,000 cc. of urine. During the same period five examinations gave negative results. On May 14 and May 17, 1928, and May 16, 1931, respectively, 0.14, 0.23 and 0.06 mg. of lead was found in the urine. The patient, since her first visit, had used arsenic-free spring water and had had two courses of sodium thiosulphate. Four injections of 1 Gm. each were given in May, 1927, and nine injections in May, 1930. As the tests showed, she still retained arsenic and excreted it intermittently. The patient has not made a satisfactory response. We have sought additional etiologic factors in vain, and have been forced to conclude that many of these changes represent permanent injury to the nervous and vascular systems. She is not yet free from arsenic.

Case 24.—A man, aged 35, came to the clinic on Feb. 13, 1930. The family history was without significance. Without previous illness of consequence, numbness of both feet developed in June, 1929. A month later, the legs became weak, and by Dec. 1, 1929, he had bilateral foot drop. About three weeks before registration, numbness began in the hands and the strength of the grip diminished.

General examination did not reveal any abnormality. Function of the cranial nerves was normal. There was decided reduction in the strength of both legs, with foot drop. The hands were weak. The reflexes of the arms were obtained. The knee jerks were reduced markedly and the achilles reflexes were absent. Joint sense was lost in the feet, and vibratory sense was greatly reduced. The muscles of the calves were not abnormally sensitive to pressure. There was slight reduction of superficial sensibility over the feet. On Feb. 17, 20, 22, 25 and 27, 1930, respectively, chemical tests gave evidence of 2.5, 0, 0, 10.0 and 1.9 mg. for each 1,000 cc. of urine. One gram of hair contained 0.02 mg. of arsenic. The patient was accompanied by a friend who lived in the same household, and his urine was also tested for arsenic on February 22 and 24, and was found to contain 34 and 23 mg. to the liter. Here again, the companion excreted much larger amounts of arsenic than the patient; only the patient suffered from multiple neuritis.

Case 18.—A man, aged 39, came to the Mayo Clinic on Feb. 23, 1927. His family history was without significance. About September, 1924, a numb sensation had appeared in the toes, and had persisted and gradually extended to above the knees. Associated with this, ataxia had developed, and the position sense had been reduced in the legs. In September, 1926, paresthesia had begun in the fingers and in the hands, and occasional fibrillary twitchings had been felt in the muscles of the back and of the abdomen. He had taken some arsenic during the course of the illness, but was unable to give the precise period or dosage. He had had no pain.

General and laboratory examinations gave negative results. The urine, blood count, vision and eyegrounds, nose and throat and basal metabolic rate were nor-

mal. The patient had two infected teeth. The cranial nerves were normal. The strength of the arms was normal, but the legs were decidedly weak, and there was some atrophy about the peroneal groups. A few fibrillary twitchings were seen about the arms and legs. The brachial reflexes were normal. The knee and achilles reflexes were absent. The plantar response was slightly flexor in nature. The joint and vibratory sensations were abolished in the feet, but were normal in the hands. Pressure pain was decidedly increased. Pain, temperature and tactile sensations were moderately reduced in the legs, increasing distally. On March 1, a twenty-four hour sample of urine contained 16 mg. of arsenic and no lead. Eighteen subsequent examinations were made, the last on Dec. 26, 1927. In twelve of these, lead was found in amounts varying from 0.38 to 0.63 mg. in the samples tested. Six negative tests were distributed irregularly during this period. On July 28, 1927, the urine of the patient's wife was tested, and we found that it contained 0.59 mg. in each sample. At no time during our observations was arsenic again found in the patient's urine. The drinking water from the patient's home was found to contain 0.07 mg. for each gallon (4 liters). This amount would appear to be too dilute to have furnished the amounts found in the urine. On treatment for the elimination of lead the patient made a tardy but satisfactory recovery. We were inclined to look on this case of multiple neuritis as being due to lead; however, one may speculate with interest on the significance of the arsenic in the first specimen. Probably both persons were exposed to similar amounts of lead, yet only the husband gave evidence of structural injury.

CASE 26.—A woman, aged 46, came to the clinic on Feb. 10, 1930. In February, 1929, she had Vincent's angina, for which she received two intravenous injections of arsphenamine. Dermatitis followed. On Oct. 31, 1929, she had an attack of nausea and vomiting which lasted two days. On December 25, she again had an attack of nausea and vomiting for a day or more. About a week later, a generalized reddish rash developed and persisted for about a month. On January 23, she was again affected with vomiting, and was ill in bed for two weeks. Vomiting occurred every two or three days. There was no pain, nor was she aware of any unusual alteration of her diet.

A general examination was made at the clinic on February 10, and gave negative results in every particular. The laboratory tests gave normal results as did an analysis of gastric content and roentgenologic examination of the stomach. On February 20, the patient returned, with vomiting, and was treated in the hospital from February 21 to March 6, with subsidence of the symptoms. While she was in the hospital during this visit, soreness of the legs developed, with numbness and tingling; there were also some of these manifestations in the hands. In April, definite weakness began, and difficulty in walking developed. On May 14, a neurologic examination was made, which gave definite evidence of multiple neuritis. The cranial nerves were normal. There was decided weakness of the legs. The brachial reflexes were present, but the knee and achilles reflexes were absent. Vibratory sense was much reduced in the legs. Joint sense was abolished. The muscles of the calves were decidedly tender, and there was diminution of superficial sensibility in the legs, increasing distally.

Chemical urinalysis was done on May 16, and Nov. 5, 7 and 11, 1930, and yielded, respectively, 1.92, 5.0, 1.25 and 1.86 mg. of arsenic for each 1,000 cc. On November 7, 1.2 mg. of lead for each 1,000 cc. was found. Two other examinations gave negative results. Subsequent to the examination in May, moderate, diffuse pigmentation of the skin developed. This was still present on examination on Jan. 6, 1931, although less intense, and there was also some roughness of the palms.

By the time of this examination the patient had definitely improved, and was able to walk without much difficulty, although the physical signs of neuritis were still present.

CASE 27.—A man, the husband of the woman in case 26, aged 49, came to the clinic on Nov. 4, 1930. The family history was without significance. Five weeks before registration, the patient had what was called "stomach flu," which was characterized by nausea, vomiting and malaise, and continued for two weeks. Then, about a week later, the hands and feet began to feel numb and stiff, and shortly afterward this was followed by weakness of both extremities and uncertainty of gait.

The results of general and laboratory examination were negative. The culture of the throat was negative for diphtheria. The cranial nerves were normal. There was decided weakness of the arms and even more weakness of the legs. The patient could scarcely walk. The brachial reflexes were present, but the knee and achilles reflexes were absent. Joint sense in the toes and fingers was decidedly reduced; vibratory sense was lost in the legs and much reduced in the hands. Pressure pain was increased moderately, and there was decided sensitiveness to pressure over the soles of the feet. The gait was very ataxic. There was definite pigmentation of the skin, with scattered black freckles. There was slight edema of the skin about the ankles and in the muscles of the calf. On November 13, 1.0 mg. of arsenic was found in 1,000 cc. of urine; there was no lead. On January 6, the urine was negative for arsenic and lead. The well water at the patient's home contained 0.01 mg. of arsenic for each liter. On January 6, the physical weakness and ataxia had increased considerably, and the patient was confined to a wheel-chair. The pigmentation was slightly more intense. Reports received on April 25, 1931, indicated that the patient is gradually improving.

It is only presumptive evidence that this man and his wife (cases 27 and 26, respectively) received considerable amounts of arsenic at intervals, since both had had marked gastric symptoms followed by neuritis. We were unable to obtain any clue to its probable source. The arsenic content of the well water was evidently not sufficient to account for such effects.

ABSTRACT OF DISCUSSION

DR. GEORGE A. MOLEEN, Denver: Were there any changes in the eyegrounds?

DR. W. D. SHELDEN: No, there were no changes.

THE BLOOD PRESSURE IN SCHIZOPHRENIA*

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Numerous observers have noted that the arterial tension in dementia praecox is below that of the average person. Kraepelin [1] stated that the blood pressure in this condition, as a rule, is lowered. Besta,[2] in an investigation of the methylene blue excretion in this psychosis, noted that the arterial pressure is below normal. Gibson,[3] conducting an examination of the pathologic features of dementia praecox, found the mean systolic pressure in 44 male patients to range between 113 and 118 mm. of mercury among the various types, with 4 catatonic, 2 hebephrenic and 2 paranoid subjects having a systolic tension less than 100. Dawson [4] reported 50 cases of dementia praecox (in males) in which the mean systolic level was 116.9 mm., with 10 cases of catatonia and 4 of hebephrenia in which it was below 100; the diastolic reading was between 55 and 65 mm. in all cases. In 25 male schizophrenic patients, whose pressure was reported by Kanner,[5] the mean systolic point was 116.8 mm. Weber [6] cited 15 male patients suffering from this psychosis, whose mean systolic pressure was 108.5 mm., with a pulse pressure of 45.1. An interesting case was presented by Raphael, Parsons and Woodwell [7] of a boy who, during an acute catatonic phase, had

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1. Kraepelin, E.: Dementia Praecox and Paraphrenia, translated by R. Mary Barclay, edited by G. M. Robertson, Chicago, Chicago Medical Book Company, 1919.

2. Besta, C.: Sul rapporto fra altezza della pressione sanguigna e rapidita di eliminazione del bleu di metilene nello demenza precoce, Riforma med. **23**:204, 1907.

3. Gibson, G. H. R.: The Pathology of Dementia Praecox, Especially in Relation to the Circulatory Change, Arch. Neurol. & Psychiat. Path. Lab. Lond., **5**:182, 1911.

4. Dawson, W. S.: A Study of Endocrine-Autonomic Disorders of Dementia Praecox, J. Ment. Sc. **69**:182 (April) 1923.

5. Kanner, L.: The Adrenalin Blood Pressure Curves in Dementia Praecox and the Emotional Psychoses, Am. J. Psychiat. **8**:75 (July) 1928.

6. Weber, P.: Blutdruckmessungen bei Kranken mit manischdepressiven Irresein und Dementia praecox, Arch. f. Psychiat. **47**:391, 1910.

7. Raphael, T.; Parsons, J. P., and Woodwell, M. N.: Schizophrenic Catatonia with Associated Metabolic and Vegetative Features, Arch. Neurol. & Psychiat. **9**: 471 (April) 1923.

a systolic pressure of from 90 to 100 mm, which on recovery rose to 120. Five catatonic patients, studied by Walther,[8] had a mean systolic level of 110.2 mm. In Langfeldt's[9] excellent monograph, the mean pressure in 28 male schizophrenic persons was reported to be 116.2, while that of the controls was 125.2 mm. Furthermore, Cornell[10] stated that in 25 cases the average systolic pressure was 115 mm. while sitting and 95 mm. while reclining. On the other hand, the observations of Parkin[11] in 89 cases revealed a mean systolic pressure of 123.3 mm., and in Paddle's[12] 90 schizophrenic males the mean systolic pressure was 134.6. Finally, in Gibson and Kimberly's[13] series, the 29 male patients had a pressure of 159, systolic, and 87, diastolic, but the subjects were 60 years of age or over, and all but one presented evidences of cardiorenal disease.

Comparable studies of blood pressure in normal subjects are included in the numerous statistical reports on life insurance applicants and on college students. Lee[14] found that in a routine examination of freshmen at Harvard College the mean systolic pressure was 120 mm. and the mean diastolic was 80. Alvarez,[15] in a study of first year students at the University of California, placed the average systolic level at 126 mm. In a later study with Stanley,[16] of 6,000 prisoners, the mean systolic reading was found to be 118.5 mm., while in 442 guards the mean systolic pressure was 133.5 mm. The lower level in the prisoners was attributed to basality of environment and to freedom from financial stress and strain. Hunter[17] noted that between the ages of 17 and 32 the systolic pressure varies between 120 and 126 mm. Fraser and Col-

8. Walther, F.: Ueber das Verhalten von Pulszahl und Blutdruck beim Katatoniker im übereinflüssten Zustand und im pharmakologischen Versuch, Arch. f. Psychiat. **89**:377, 1930.

9. Langfeldt, G.: The Endocrine Glands and Autonomic Systems in Dementia Praecox, Bergen, J. W. Eides Boktrykkeri, 1926.

10. Cornell, W. B.: Cyanosis in Dementia Praecox, J. A. M. A. **59**:2208 (Dec. 21) 1912.

11. Parkin, G. G.: Some Observations on the Study of the Blood Pressure in the Insane, J. Ment. Sc. **73**:240 (April) 1927.

12. Paddle, K. C. L.: A Review of Blood Pressures in the Insane, J. Ment. Sc. **74**:733, 1928.

13. Gibson, E. T., and Kimberly, A. M.: Blood Pressure in Insane Patients Aged Sixty and Over, Boston M. & S. J. **179**:693, 1918.

14. Lee, R. I.: Blood Pressure Determinations, Urinary Findings, and Differential Blood Counts in a Group of 662 Young Male Adults, Boston M. & S. J. **183**:541, 1915.

15. Alvarez, W. C.: Blood Pressure in University Freshmen and Office Patients, Arch. Int. Med. **26**:381 (Oct.) 1920.

16. Alvarez, W. C., and Stanley, L. L.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards, Arch. Int. Med. **46**:17 (July) 1930.

17. Hunter, A.: Proc. A. Life Insur. M. Dir. North America **7**:153, 1920.

well [18] took the pressures of large groups of soldiers, their levels being from 110 to 120 mm. systolic, and from 70 to 80 mm. diastolic. Symonds,[19] dealing with 150,000 life insurance applicants, placed the systolic pressure at 127.6 mm. and the diastolic at 83.5 mm. Schneider and Truesdell [20] reported a group of 2,000 unselected cases in which the mean reclining systolic pressure was 118 and the reclining diastolic 72 mm.

Most statisticians, then, consider the mean systolic pressure of the general population to be around 125 mm., and the mean diastolic about 80. The relatively few comparable studies in dementia praecox place these figures at about 115 mm. systolic and 65 mm. diastolic. It was our thought that, for a thorough statistical investigation, neither set of figures was absolutely comparable with ours, because they did not take into account the large number of adventitious factors that affect the blood pressure, such as food, exercise and emotional contacts, as well as the unavoidable errors of observation. The elimination of such variables would mean that the blood pressure would have to be taken in what is known as, essentially, the "basal" state, in which the person has not eaten for fourteen hours and previous exertion has been limited to the amount necessary for transportation to the laboratory. It is under such conditions [21] that the present study has been made both with the patients and with the normal control subjects. Of the former, there are 180 (male) with dementia praecox, definitely diagnosed by the psychiatric staff of the Worcester State Hospital, under no treatment except the usual psychiatric routine therapy. For controls, there are the records of 323 first year students of the Boston University School of Medicine, which have been loaned to us through the courtesy of Dr. A. W. Rowe of the Evans Memorial of that institution. The students probably constitute a fair sample of the normal, healthy community. Among the patients, thorough physical and laboratory examinations have secured the elimination of all suffering from any chronic or acute organic ailment. In both groups, the readings were taken by means of a standard mercury sphygmomanometer, with the exception of about 5 per cent of the patients, with whom a Tycos self-recording instrument was used. No similar work has been done, so far as our search of the

18. Fraser, J., and Colwell, E. M.: Clinical Study of Blood Pressure in Normal Conditions, J. A. M. A. **70**:520 (Feb. 28) 1918.

19. Symonds, B.: The Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232 (Jan. 27) 1923.

20. Schneider, E. C., and Truesdell, D.: A Statistical Study of the Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing, and After a Standard Exercise, Am. J. Physiol. **61**:429, 1922.

21. In addition, in the controls there was the additional energy required for putting on clothing.

literature has revealed, with any schizophrenic patients, and the sole similar work on a normal group is that reported by Addis,[22] embracing 89 observations on 76 soldiers, in whom the blood pressure was taken early in the morning before the soldier had arisen or even in many cases awakened, and in which the readings were 99 mm. systolic, and 71 mm. diastolic. He also made 300 observations on 300 soldiers at varying times during the day and found the mean pressure to be 127 systolic and 78 diastolic.

OBSERVATIONS

The results of our study are shown in table 1 and the accompanying charts. Approximately 45 per cent of the patients have had two or more pressures taken under basal conditions owing to discharges and subsequent reentries. In these cases, the mean of the readings has been taken.

TABLE 1.—*Comparison of Data on Blood Pressures of Patients with Dementia Praecox and Students (Controls)*

Blood Pressure	Number of Persons	Maximum, Mm.	Maximum, Mm.	Range, Mm.	Mean, Mm.	Standard Deviation	Coefficient of Variation
Systolic.....	Patients 180	65	162	97	104.5 + 0.74	14.75 + 0.52	14.1%
	Students 323	90	153	63	115.7 + 0.37	9.93 + 0.26	8.6%
Diastolic.....	Patients 180	16	85	69	54.5 + 0.62	12.4 + 0.44	22.7%
	Students 323	32	93	61	71.2 + 0.32	8.7 + 0.23	12.2%
Differences.....	Systolic, Students — Patients = 11.2 + 0.82 mm.						
	Diastolic, Students — Patients = 16.7 + 0.69 mm.						

In the patients, the mean systolic tension was 104.5 ± 0.74 mm.; in the students, it was 115.7 ± 0.37 mm. There is seen to be a difference of 11.2 ± 0.82 mm. of mercury. Such a variation, representing conditions as standardized and uniform as could be obtained, is presumably of more significance than the variations secured under the irregular conditions mentioned in the previous reports.

A comparison of two central tendencies, however, is of little value without knowing the degree of variability of the separate measures. This is furnished by the calculation of the coefficient of variation. In the patients this figure is 14.1 per cent, while in the controls it is 8.6 per cent, showing a variability of definitely greater magnitude in the patients' systolic readings than in those of the students. This tendency is also shown by the broader range and greater standard deviation of the patients. It has been noted by both Kraepelin [1] and Enebuska [23] that

22. Addis, T.: Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29**:539 (April) 1922.

23. Enebuska, C. J.: Von der vasomotorischen Unruhe bei Geisteskranken, Ztschr. f. d. ges. Neurol. u. Psychiat. **34**:449, 1916.

the blood pressure in this disease shows marked lability. Whether this is representative or is due chiefly to the small number of patients in this study, only more extensive work will reveal.

We turn next to a consideration of the diastolic pressures. In the patients, this was 54.5. ± 0.62 mm.; in the students, 71.2 ± 0.32, a difference of 16.7 ± 0.69. Theoretically, the diastolic level is subject to less fluctuation from environmental factors than is the systolic; a significant difference in this reading between psychotic and normal subjects would seem, then, to be of even greater importance than in the systolic. Actually, however, the diastolic readings in this series were approximately 50 per cent more variable than the systolic, not only in

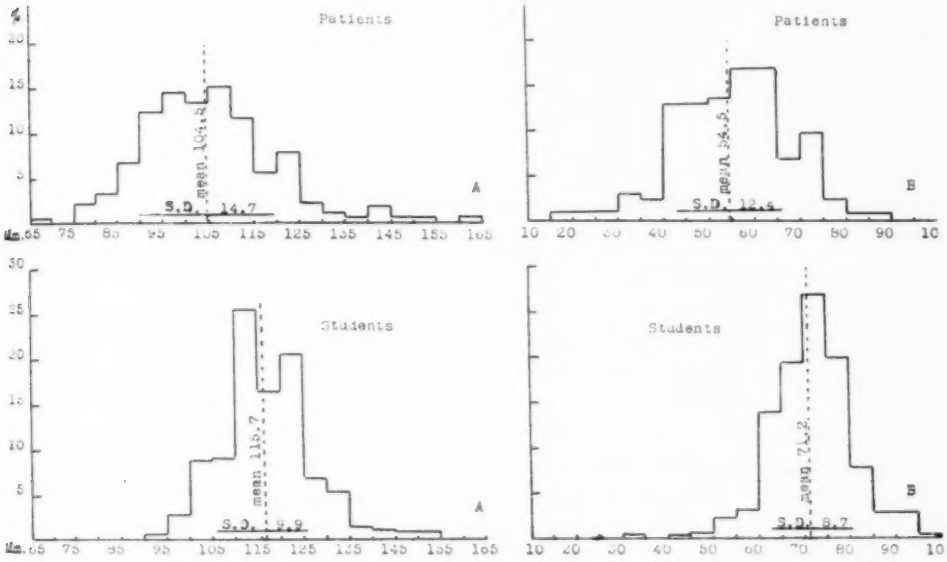

Chart 1.—Distribution of systolic (*A*) and diastolic (*B*) blood pressures in 323 medical students and 180 patients with dementia praecox. The ordinates represent the percentages of frequency; the abscissas, the blood pressures in millimeters.

the patients but also in the students. Again, variability of the diastolic pressures of the patients was significantly higher than that of the controls. Whether this greater variability mirrors an inherent lability in the cardiovascular controlling mechanisms cannot, at this point be determined. That there is greater technical error in the reading of the diastolic level than the systolic is demonstrated by a check experiment described in a subsequent section. When due allowance has been made for errors of observation, however, the data recorded indicate a lowering of vasomotor tone in the patients. What relation this low diastolic level may have to the state of the cardiovascular apparatus will be discussed in a later paragraph.

Two problems arise from a consideration of the foregoing data: (1) the degree of technical error involved in the method of taking the blood pressure (the method used for checking this was suggested by E. M. Jellinek, statistician); (2) the difference in readings under basal and nonbasal conditions. In the first case, an evaluation of the errors of reading was made by taking blood pressures in 47 cases by means of a multiple stethoscope, permitting 4 people to listen at the same time. These four included two of us (H. F. and F. H. S.), the technician (A. W.), who has routinely taken the pressures on the patients, and another member of the research service (J. R. L.). The technic of placing the systolic pressure as the point at which the first clear sound was heard was used by all. As the technician determined the diastolic pressure at the level of the last sound heard, and as the authors customarily take it as the point of change from the clear to the dull phase, it was decided that one half of the group should use the former and the other half the latter method of reading the diastolic pressure.

TABLE 2.—*Blood Pressure of Patients with Dementia Praecox as Determined by Four Observers*

Observer	Mean Systolic Pressure, Mm.	Mean Diastolic Pressure, Mm.
H. F.	114.5	72.6
J. R. L.	115.7	73.8
F. H. S.	115.3	70.8
A. W.	115.2	70.6

The results of this experiment showed that in the systolic determinations there were 10 cases of perfect agreement, i. e., among all the listeners, and in diastolic readings, none; in the systolic determinations there were 5 cases of perfect disagreement, and in the diastolic determinations, 17. It is obvious that the accuracy of the diastolic readings is significantly less than that of the systolic. In table 2, it is seen that in reading the systolic pressures the average error was about 2 mm., and in reading the diastolic pressures it was about 5 mm. The first pair of observers, who took as the diastolic point the change in sound, had as their mean diastolic 74.2 mm., as compared with the 70.7 mm. obtained with the other method. It is evident, then, that this change in technic (ignoring the personal factor) involves a difference of about 4 mm.

As regards the pressures of the control group of students, the method of reading the diastolic level was that of taking the change of sound, and the first 50 cases were checked by one of us. The technic in determining the diastolic reading differed, then, somewhat in the two groups, and on the basis of the figures derived from the experiment

this would account for about 4 mm. in the difference between diastolic pressures in the two samples.

It was stated previously that the blood pressures in this study were taken under basal conditions to eliminate as far as possible the variable effects of food, exercise and time of day. Addis [22] found a mean difference of 28 points in the systolic and 7 points in the diastolic as a result of a comparison of basal and nonbasal pressures. The mean blood pressure of our controls (115.7 systolic and 71.2 diastolic) is almost identical with that of Schneider and Truesdell,[20] 117.9 systolic and 71.6 diastolic, and not far different from Alvarez and Stanley's [16] figure of 118.5 mm. systolic and from 68 to 70 mm. diastolic. On the other hand, the statistical validity of the mean determinations based on 150,000 life insurance applicants is probably great, and their mean pressures were 127.6 systolic and 83.5 diastolic. To evaluate this factor in our dementia praecox population, a group of cases studied by J. R. Linton, a member of the Research Staff, was utilized. There were 84 observations on 49 subjects, taken on the same day under morning basal conditions, and in the afternoon. The mean systolic level in the afternoon was greater by 3.7 mm., and the mean diastolic was less by 1.3 mm., differences of practically no importance. It should be said that in the cases of Alvarez and Stanley,[16] Schneider and Truesdell [20] and Linton, the patients were all given a rest period varying from five to sixty minutes before the nonbasal pressures were read; possibly an important factor. The evidence is not, of course, conclusive, but does suggest that the determination of mean pressures in a large group of cases, and possibly only in dementia praecox, is not affected to a great extent by the factors of food, exercise and time of day, provided that the patients are given a rest period previous to the taking of the blood pressures.

A brief consideration of the pulse pressure is of interest. In the students, this is 44.5 mm., and in the psychotic patients 50 mm. The greater pulse pressure of the patients is due primarily to the greater difference in the diastolic points. This difference of 5.5 mm. is statistically significant, as it is derived from two measures in which the variation from the controls is valid. Its physiologic importance is not so easily defined. Whether this greater pulse pressure in the patients means that the cardiovascular apparatus labors under a greater load is somewhat questionable. The statistical analysis of the data brings forth two facts of interest. Although pulse pressure is generally positively correlated with systolic blood pressure, if the means of various samples of normal controls and schizophrenic patients are taken, the correlation will tend to be inverse, for, while the systolic pressures are higher in the students, their pulse pressures are lower. Furthermore, correla-

tion between systolic and diastolic blood pressure is less exact in normal than in schizophrenic persons. A computation of the coefficients of correlation for both cases shows the following constants:

Patients ..... $r = 0.62 \pm 0.3$
Students ..... $r = 0.43 \pm 0.03$

The difference appears even greater when stated in terms of percentage variation covered. In schizophrenic patients, the variation in one variable accounts for 22 per cent of that in the other variable, while in normal persons only 10 per cent of the variation in the one variable is covered by the variation in the other variable.

It has been accepted that blood pressure varies directly with age. Of late, however, the observations of several investigators have shown this to be not entirely true. In children up to the age of 15, there has been shown to be a distinct correlation between age and both systolic and diastolic pressures.[24] The case is somewhat different for adults. Alvarez and Stanley [16] found no change in the systolic pressure up to the age of 40, and after that a direct tendency to rise. Symonds [19] concurred in this view, but, in addition, an analysis of his figures shows a steady rise in the diastolic level beginning at 20 years. Huber [25] stated that age has "no statistical significance" in the determination of systolic pressures, and Dunham's [26] systolic levels vary but 5 mm. from the second to the fourth decade. It seems the consensus, therefore, that while there is a rise in systolic pressure in childhood and after the onset of middle age, there is little change between these periods, but that the diastolic level tends to increase steadily throughout. A study of figure 2 shows practically no tendency for the systolic or for the diastolic pressure to vary directly with age. After the age of 50, however, there are a few readings that suggest a rising tendency, more marked in the systolic than in the diastolic pressure. This is probably to be expected with the onset of degenerative processes in the cardiovascular apparatus.

A further analysis of the figures was made to determine whether any correlation exists between height and blood pressure. No positive relationship could be detected. A glance at figure 3 shows no constant change in either systolic or diastolic pressure. The extremes in the patients present a variation in pressure that might be considered almost as being conditioned by the heights of those persons, but the

24. Wolfensohn-Kriss, P.: Ueber den Blutdruck im Kindesalter, Arch. f. Kinderh. **53**:332, 1910.

25. Huber, E. G.: Systolic Blood Pressures of Healthy Adults in Relation to Body Weight, J. A. M. A. **88**:1554 (May 14) 1927.

26. Dunham, G. C.: Variation in Blood-Pressure as Associated with Variation in Age and Body-Weight, Internat. Clin. **3**:81 (Sept.) 1925.

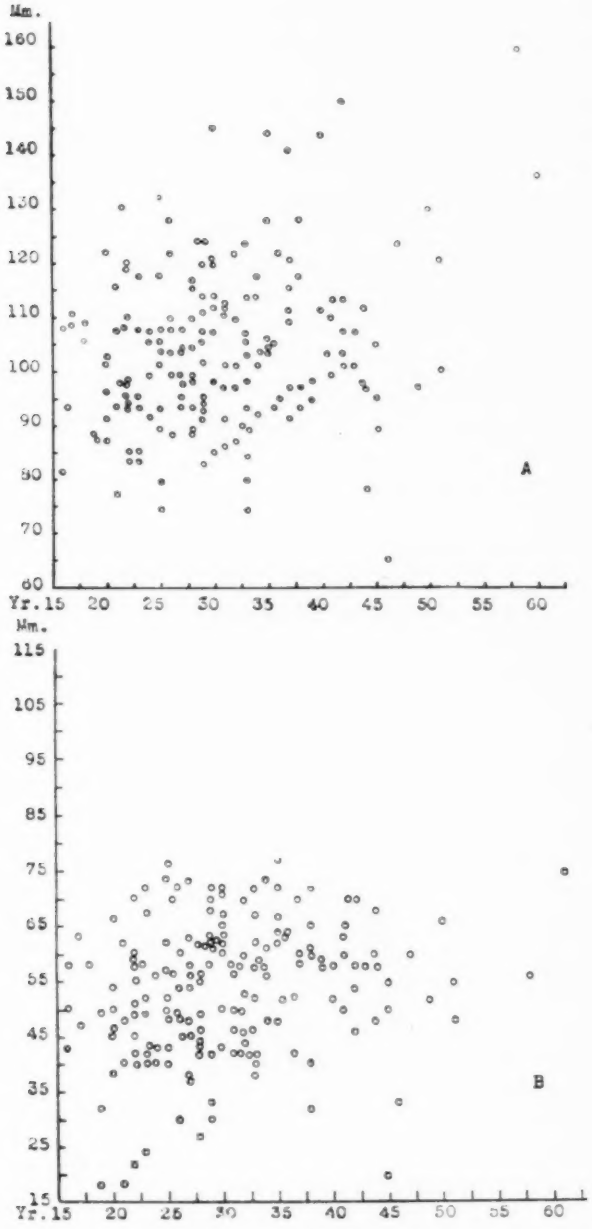

Chart 2.—Systolic (*A*) and diastolic (*B*) blood pressures according to age.

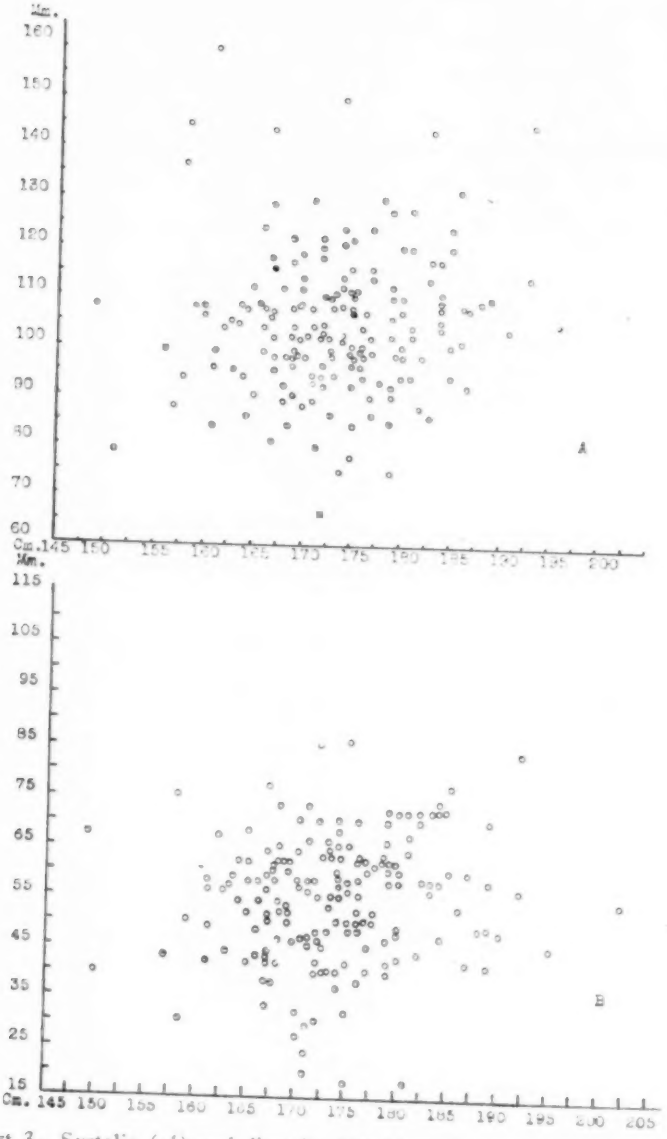

Chart 3.—Systolic (*A*) and diastolic (*B*) blood pressures according to height. The ordinates represent blood pressures in millimeters; the abscissas, heights in centimeters.

cases are too few for this tendency to have any but minor significance. The lack of such a correlation in adults, as shown by this study, is confirmed by the conclusions of Huber,[25] Alvarez and Stanley[16] and others.

The effect of weight on blood pressure was next investigated. In children, the arterial pressure varies directly with the weight.[24] In adults, Symonds[19] recorded a rise of 12 mm. in the systolic levels between the extremes of 35 per cent underweight and 50 per cent overweight. Dunham[26] noted a slight rise in both systolic and diastolic levels with weight above normal; there is no fall in pressure as the weight goes below this point. Huber,[25] on the other hand, stated that underweight and hypotension are more closely related than overweight and hypertension. Alvarez and Stanley[16] found that weight has little effect on blood pressure until the age of 35; then fatness increases and leanness decreases arterial pressure.

In our series (fig. 4), nutrition was expressed not merely in terms of weight, but as coefficients of both age and height. The normal figures were derived from the tables of the Metropolitan Life Insurance Company, and the proportion of the actual weight to the ideal figure was then obtained as a nutritional percentage. In the patients, no correlation with weight was obtained with either modality of pressure. The nutrition of the patients is, on the whole, below that of the average population, the mean being 86 per cent, with only 7 per cent attaining a level of at least 100 per cent, so that this failure of correlation may be due to a lack of normal distribution of this factor.

In accordance with the usual psychiatric classification, the patients have been divided into five groups: simple, paranoid, catatonic, hebephrenic and unclassified. In some of the previous discussions on the subject of this paper, the patients have been divided in a similar manner, and, in addition, into quiescent and active stages of catatonia (an obviously unreliable subdivision). Gibson and Kimberly,[13] Langfeldt[9] and Parkin[11] found the highest pressures among the hebephrenic patients. An analysis of Dawson's[4] figures shows that the tension in the paranoid type is superior to that of the other types.

In the present series (fig. 5), the differences between the various types are not sufficiently large to be statistically significant. They show, however, an interesting tendency in that the paranoid group exhibits the highest level, both in systolic and diastolic readings. The catatonic group shows the lowest systolic pressure, which may be due, possibly, to the lesser degree of muscular activity displayed by that class. The diastolic pressures do not run parallel to the systolic in their respective groups, having a greater tendency to remain at a constant level.

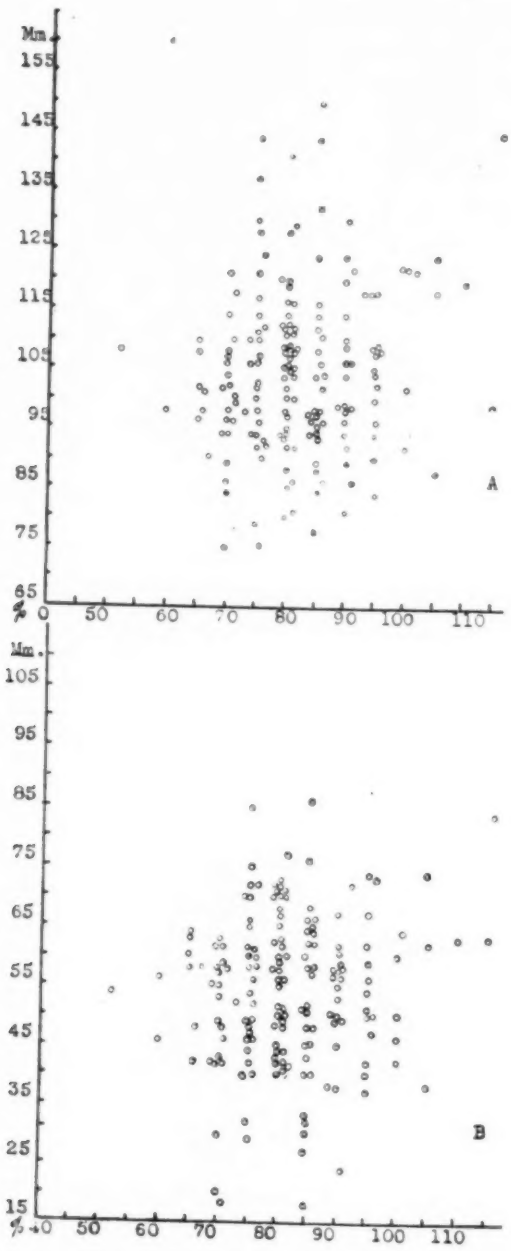

Chart 4.—Systolic (*A*) and diastolic (*B*) blood pressures according to nutritional percentages. The figures for normal weights according to heights were obtained from the Metropolitan Life Insurance Company, and the proportion of the actual weight of the patient as related to the ideal figure for his height was obtained as a percentage.

Much has been written concerning the influence of climate on blood pressure. Studies of Cantonese [27] and Filipinos [28] have shown a general lowering of the blood pressure, as compared with that of inhabitants of the western continents. Furthermore, according to Foster,[29] white foreigners in these areas have displayed this same tendency, which becomes more marked the longer the stay in the tropics. Alvarez,[15] too, noted an average increase of 5 mm. in the systolic pressure on cooler days. Chamberlain [30] dissented from the observations cited. He detected no change in the systolic pressures of American soldiers in the Philippines, certainly not during a residence of

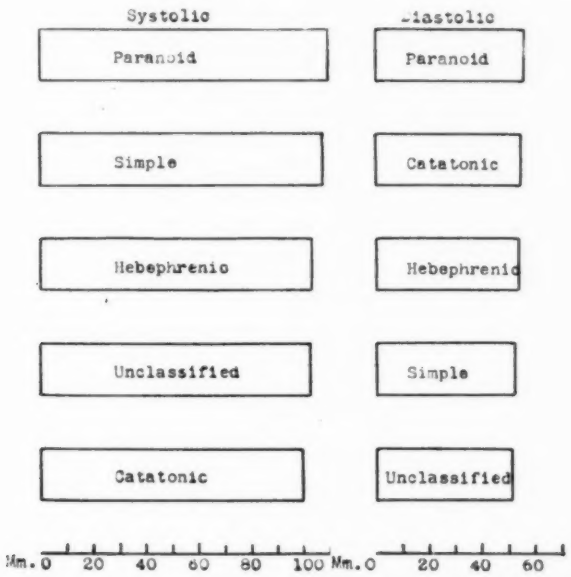

Chart 5.—Mean systolic and diastolic blood pressures according to the type of psychosis.

three years, nor was there any appreciable difference between the pressures of American and native soldiers. The majority of investigators, however, find a tendency to hypotension in warmer climates. Whether this is to be ascribed to racial factors or to the lessened

27. Cadbury, W. W.: The Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362 (Sept.) 1922.

28. Musgrave, W. E., and Sison, A. G.: Philippine J. Sc. **5**:325, 1910.

29. Foster, J. H.: The Blood Pressure of Foreigners in China, Arch. Int. Med. **40**:35 (July) 1927.

30. Chamberlain, W. P.: A Study of the Systolic Blood Pressure and the Pulse Rate of Healthy Adult Males in the Philippines, Philippine J. Sc. **6**:467 (Dec.) 1911.

activity in those countries will not be discussed here. In the present series (fig. 6), each reentry was counted so that the total number of measures is increased. No constant variation in systolic pressure was found with temperature; the lowest levels occur in March and September, while the highest points fall in February, May and November. A similar lack of conformity is presented by the diastolic pressures. It is possible that the relatively sedentary life of the patients, with their lack of participation in outdoor winter activities, may be a factor in ironing out any elevation that might otherwise have occurred in colder weather. On the other hand, the chart presents, in the systolic pressures, a tendency to a series of curves that suggests the possibility of some inherent rhythmic periodicity of arterial tension, which warrants further investigation.

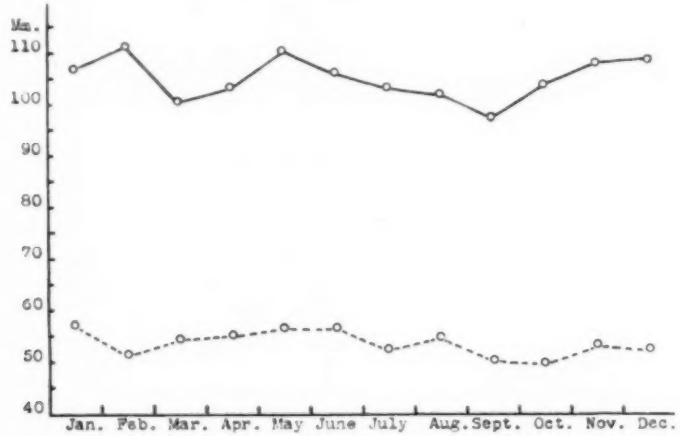

Chart 6.—Systolic (——) and diastolic (- - - -) blood pressures according to season.

A possible correlation was sought between the height of the blood pressure and the length of the institutional stay (fig. 7). It might be expected on the basis of freedom from mental and physical stress that the arterial tension would adjust itself at a lower level. This is not borne out in this study. The pressures, both systolic and pulse, fluctuate, but generally around a constant figure, except for the persons who have been confined to the hospital for at least ten years. At that point, the levels begin to rise, but this is probably due to the entrance of another factor, arteriosclerosis, for all the patients are in the fifth or later decades of life. It is probable, then, that the height of the blood pressure has no relationship to the duration of institutionalization, although the latter may tend to stabilize it and to delay the onset of hypertension through the avoidance of environmental strains.

Another possible association was sought between the blood pressure and the total daily output of nitrogen. This may be considered as one index of renal efficiency from the point of view of excretion. None of our patients showed any signs of impaired renal function, at least so far as could be demonstrated by microscopic, chemical and excretory studies, so that little information could be expected from such a study. It is also unfortunate that no relationship can be demonstrated between

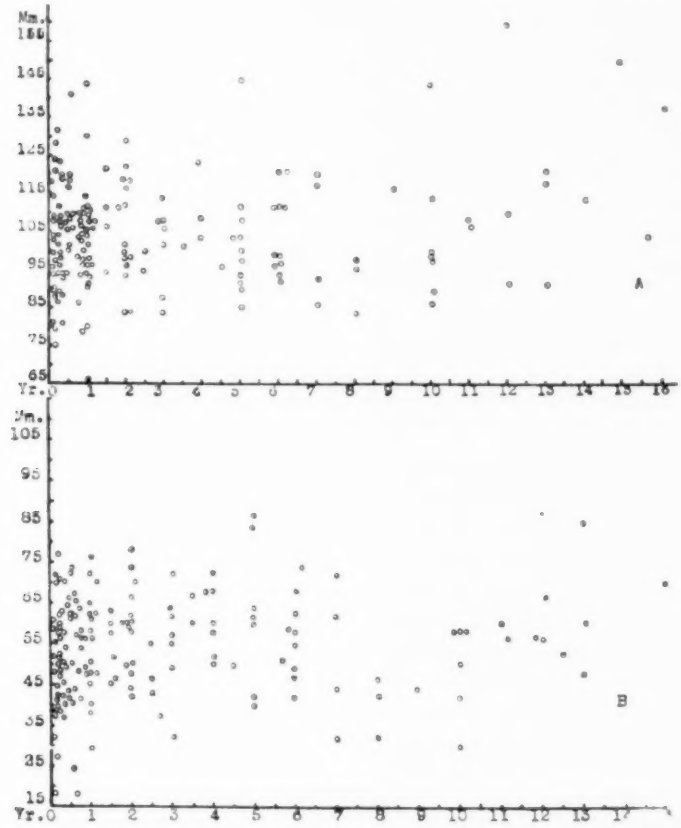

Chart 7.—Systolic (*A*) and diastolic (*B*) blood pressures according to years of hospitalization.

the protein intake and the total nitrogen output, for the patients were not on weighed diets. At any rate, no correlation was found between these two factors (fig. 8). The total nitrogen output varied from 5 to 17 Gm. daily. The normal figure is approximately 12 Gm.,[31] but

31. Rowe, A. W.; Chandler, J.; Proctor, B. E., and Greene, W. B.: Vital Function Studies: II. A Group Study of Certain Blood and Urine Findings, and of the Gaseous Metabolism, Boston M. & S. J. **192**:747 (April 16) 1925.

in the patients the modal value was from 9 to 10 Gm. This difference may be due to the lesser proportion of protein in the hospital diets, the daily ration of protein being from 75 to 90 Gm., as compared with about 100 Gm. consumed by the average person on the outside. The cause for the variation is not definitely known. It is not due to errors of collection, for this figure is checked by all the other nitrogenous elements of the urine, and an incomplete sample is easily detected.[32] It

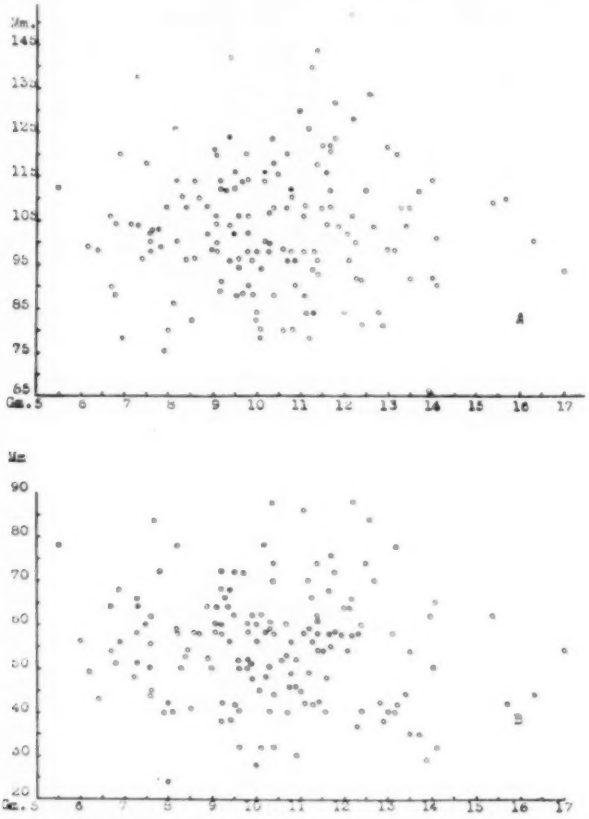

Chart 8.—Systolic (*A*) and diastolic (*B*) blood pressures according to total daily nitrogen output in grams.

is more likely to be dependent on variations in the protein intake of the different persons.

COMMENT

The preceding paragraphs have brought out two positive facts concerning the blood pressure in dementia praecox, namely, a decrease in

32. The authors have arbitrarily set as their normal values for the daily creatinine output, from 0.35 to 0.55 Gm. Samples of urine in which the creatinine values lay beyond these limits were not considered in this study.

the systolic tension and a fall in the diastolic level. The statistical limitations of these observations have been discussed. It is not to be expected, either from the small number of cases or from the nature of the physiologic processes involved, that these figures will satisfy rigid statistical standards; they are offered merely as suggestive tendencies, based, however, on carefully maintained methods of procedure.

Turning to an interpretation of the results, we find several possible explanations. The nutrition of the patients should first be considered. It is 14 per cent below that of the average person, and despite the lack of correlation of our observations, the relative malnutrition of psychotic persons as a factor in the production of low blood pressure is worthy of consideration.

It is well known that the death rate from tuberculosis is much higher in the group with dementia praecox than in that of the population at large. At St. Elizabeth's Hospital,[33] the latest figures show that among patients with dementia praecox there are 317 cases of active tuberculosis per thousand. While none of our patients showed, either in physical, laboratory or roentgen examination, any signs of such activity, many of them have latent or healed processes, which have possibly a depressant effect on the blood pressure.

The patients in this institution, as in other psychiatric institutions, tend to have a lessened degree of muscular activity. Although they are encouraged to undertake a moderate degree of labor, the number responding to such suggestions is only about one half. The medical students, also, lead a somewhat sedentary existence, but in them there is a further factor of mental strain not present in the patients, although in the latter the emotional content of their hallucinations and delusions might tend to elevate their blood pressures.

The rôle of the constitutional factor in the maintenance of blood pressure has been reviewed by Alvarez and Stanley,[16] who found no difference in the tensions of the various bodily types and disclaimed any importance for this factor. Larimore,[34] in a study of factory workers, recorded a difference of 20 mm. between the systolic tensions of sthenics and asthenics. Fossier,[35] too, stated that hypotension is usually found in the asthenic or splanchnoptotic type. If this claim is valid, it may well be of some value in the interpretation of our results, for, in schizophrenia, the patients are, according to Raphael, Ferguson

33. U. S. Dept. Int., St. Elizabeth's Hosp., Bull. no. 6, July, 1930.

34. Larimore, J. W.: A Study of Blood Pressure in Relation to Types of Bodily Habitus, Arch. Int. Med. **31**:567 (April) 1923.

35. Fossier, A. E.: A Cause of Essential Hypotension, Am. J. M. Sc. **171**:496 (April) 1926.

and Searle,[36] predominantly of this type. Little stress can be laid on this point, however, for no careful anthropometric measurements were made in the present series.

Langfeldt[9] and many others have commented on the autonomic imbalance so frequently noted as a feature of this disease. The bradycardia, cyanosis, pallor and intestinal stasis so often found are all suggestive of a vagotonic condition that might well account, at least in part, for the hypotension. In this connection, it may be considered that the low diastolic pressure may be due to a diminution of the vasoconstricting effect of the sympathetic system.

A light is thrown on the situation by the pathologic studies of Lewis.[37] In dementia praecox, according to this writer, the characteristic postmortem observation is a small, hypoplastic circulatory system, with a small heart and a slender aorta. Whatever cause may be the background for this condition, it may well be a factor in the hypotonia. Incidentally, according to Lewis, paranoid subjects do not share this hypoplastic condition, although they have an unusual number of vascular lesions. Whether this fact can be correlated with the tendency to higher pressures found in this group cannot be adequately discussed in the present paper.

A final cause to be considered is the degree of endocrinopathy present in schizophrenia. All of the endocrine organs have been implicated, hypofunction being the more common finding by numerous writers, including Gibbs,[38] Lewis and Davies,[39] Hoskins[40] and Gibson.[3] In a recent paper, Hoskins and Sleeper,[41] working with essentially the same group of patients, found that 88 of 130 cases, or 68 per cent, showed more or less evidence of endocrine deficiency. This, of course, is a much higher incidence than that among the average population. In the experience of Rowe[42] and many other workers,

36. Raphael, T.; Ferguson, W. G., and Searle, O. M.: Constitutional Factors in Schizophrenia, in Association for Research in Nervous and Mental Diseases: Schizophrenia, New York, Paul B. Hoeber, 1928, p. 100.

37. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, Nervous and Mental Diseases, Monograph Series, no. 35, Washington, Nervous and Mental Disease Publishing Company, 1923.

38. Gibbs, C. E.: Sex Development and Behavior in Male Patients with Dementia Praecox, Arch. Neurol. & Psychiat. **9**:73 (Jan.) 1923.

39. Lewis, N. D. C., and Davies, Gertrude A.: A Correlative Study of Endocrine Imbalance and Mental Disease, J. Nerv. & Ment. Dis. **54**:385, 493.

40. Hoskins, R. G.: Endocrine Factors in Dementia Praecox, New England J. Med. **200**:361, 1929.

41. Hoskins, R. G., and Sleeper, F. H.: The Thyroid Factor in Dementia Praecox, Am. J. Psychiat. **10**:411 (Nov.) 1930.

42. Rowe, A. W.: Studies of the Endocrine Glands: IX. The Differential Diagnosis of Endocrine Disorders, Endocrinology **13**:327, 1929.

endocrine deficiency causes a lowering of the blood pressure, and it is probable that of all the factors hitherto considered, endocrinopathy is the most important as conducive to a condition of hypotension.

CONCLUSIONS

From a study of the basal blood pressures of 180 patients with dementia praecox, the following conclusions (as applying to this psychosis) are reached:

1. The mean systolic pressure of the patients is 11.2 mm. lower than that of normal control subjects; the diastolic pressure of the patients is 16.7 mm. below that of the controls.

2. The blood pressure does not vary with age until the fifth decade.

3. The blood pressure has no correlation with height.

4. There is no constant variation of the blood pressure with season.

5. The duration of hospitalization has no effect on the blood pressure.

6. Nutrition plays no significant rôle in the determination of the height of the blood pressure.

7. The blood pressure bears no relationship to the total daily output of nitrogen.

8. The psychotic groups vary but slightly in their mean systolic pressures; the paranoid group has the highest, and the catatonics the lowest, reading.

THE PSYCHOLEPTIC ATTACK IN THE PSYCHOSES*

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As psycholeptic attacks, Adolf Meyer singles out occurrences of considerable interest, using in a descriptive way a term employed by Janet in a part of his theory of psychasthenia. In the sense in which it is used in the Henry Phipps Psychiatric Clinic, of the Johns Hopkins Hospital, the term "psycholeptic attack," or "psycholeptic episode," refers to a sudden, vivid psychobiologic experience, with a strong somesthetic reference to the region of the head, which impresses itself on (literally, "seizes on the mind of") the patient as the critical event, or at any rate a very critical event, of his illness. This paper is an inquiry into the phenomenon as a human experience rather than as a psychologic postulate in the sense of Janet.

HISTORICAL CONSIDERATIONS

The term "psycholepsy" (Greek ψυχή, mind, and λαμβάνω, to seize on—a seizure of the mind, a fit) appears infrequently in English medical literature. Maudsley,[1] in 1887, first used the term to denote the mechanism of the attainment of supernatural knowledge by divine inspiration. He said: "The painstaking researches of pathology tend steadily to supersede an awestricken and impotent admiration of the supernatural in this its last and most obscure retreat; for they prove that in the extremest ecstasies there is neither *theolepsy* nor *diabolepsy*, nor any other *lepsy* in the sense of possession of the individual by an external power. What there truly is is a *psycholepsy*."

The use of the term so proposed by Maudsley seems to have been short-lived. It is not found in Baldwin's "Dictionary of Philosophy and Psychology," [2] in Tuke's "Dictionary of Psychological Medicine" [3] or in Skeat's "Etymological Dictionary of the English Language."[4] Bridges,[5]

* Submitted for publication, June 29, 1931.

1. Maudsley, Henry: Natural Causes and Supernatural Seemings, ed. 2, London, 1887, pt. 3, pp. 308-309 and 318.

2. Baldwin: Dictionary of Philosophy and Psychology, New York, The Macmillan Company, 1911.

3. Tuke: Dictionary of Psychological Medicine, Philadelphia, P. Blakiston's Son & Company, 1892.

4. Skeat: An Etymological Dictionary of the English Language, ed. 4, New York, Oxford University Press, 1924.

5. Bridges: Psychology—Normal and Abnormal, New York, D. Appleton and Company, 1930.

in his recent textbook of psychology, speaks of the epileptic equivalents as psycholepsy. In the American Illustrated Medical Dictionary,[6] psycholepsy is defined as "a condition in which the mental or psychologic attention is lowered." This definition is obviously an attempt to translate the French use of the word as it was introduced to modern psychology by Pierre Janet in 1903. In "Les Obsessions et la Psychasthénie," [7] Janet postulated a "psychologic tension" as a sort of energetic inner quality. This tension is of many degrees, roughly separable into high and low, with phenomena characteristic of each, forming a "hierarchy." The phenomena of the higher psychologic tension concern the perception of facts of reality and the conscious purposive activity relative to it. The phenomena of the lower psychologic tension are revery, motor agitation and certain emotions.[8] The tension oscillates normally, as seen in sleep and waking. Janet spoke of a sudden lowering of the psychologic tension as a "crise de psycholepsie." If the state of lowered tension persists, then a state of "psychasthénie" is said to exist.[9]

In 1895, Meschede [10] used the word "phrenolepsie" to denote the compulsive and irresistible character of certain types of echolalia. He had formed the word from analogy with epilepsy, catalepsy and narcolepsy (Gélineau, 1880). This word fell into disuse, but Janet retained the essential sense of Meschede's word, and thought that he was giving more precision to the idea with the use of the term "psycholepsy" to denote the sudden lowering of psychologic tension. Janet seems to have been unaware of Maudsley's earlier use of the term, which had indeed more reference to an archaic interpretation of the "sacred disease" and its correction by a psychologic term and concept.

Janet found this state of lowered tension or fitness important for his conception of the principal features of the obsessive, compulsive state as an asthenia. He also compared the psycholeptic attack with normal sleep and with epilepsy, and saw in it a sudden drop in the already existing psychasthenia. His hypothesis of the "oscillations mentales" is a basic element in his psychopathology by no means limited to psychasthenia. As a working hypothesis it is unsatisfactory because it is purely descriptive and fails to occupy itself with the human experience, with the powerful dynamic forces of the latter, and does not recognize the pluralistic approach to human problems.

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6. American Illustrated Medical Dictionary, ed. 12, Philadelphia, W. B. Saunders & Company, 1923.

7. Janet, Pierre: Les Obsessions et la Psychasthénie, ed. 2, Paris, Félix Alcan, 1908.

8. Janet (footnote 7, vol. 1, p. 506).

9. Janet (footnote 7, vol. 1, p. 511).

10. Meschede: Ueber Echolalie und Phrenolepsie, Allg. Ztschr. f. Psychiat. **53**:443, 1897.

DESCRIPTION

The psycholeptic experience may take several forms. A snapping in the head is the one most commonly described. The remarkable frequency with which this spontaneous, verbatim description is offered by patients, generally with an utter inability to enlarge on the idea, places this experience among the important symptoms of mental disease. A sharp instrument driven into the brain, a stroke of a blackjack, the currents of the brain severed by a knife stroke, a bolt of fire shooting through the brain are other versions of the episode. Janet's patient, Jean, felt something break in his head.

Often the psycholeptic attack is offered as the major complaint of the patient or as the etiologic factor or fatal turning point in his illness. The patient's statement that he was perfectly well until "something snapped" in his head is very common. The statement is usually given with a distinctly apathetic, hopeless air. Sometimes the attack is recognized as having other antecedent factors, but here the relationship ends. There is a certain insistence on its importance, its fatal quality, which leaves no doubt of the subjective value of the experience. It easily becomes the critical event of the illness to the patient.

One is impressed by the vividness of the incident. The descriptions given by the patients are confessedly inadequate. There seem to be no words to describe it. This vividness clothes it with an authority approaching what holds in some cases for hallucinations or the autochthonous ideas of the paranoiac. This vividness is doubtless intensified by the suddenness of the attack, coming on as it does without warning, like a bolt from the sky.

IMMEDIATE SEQUELAE OF THE ATTACK

The immediate results of the attack are, according to the patients, astounding. One patient, struck as by a sharp instrument driven into the occiput, was whirled around, and "things were in a turmoil, and rushed by" him for two days. Another, who felt the currents of his brain suddenly cut by a knife stroke, felt "when the ends came together they did not connect up." Another, playing cards, seemed to lose clear consciousness and was much frightened by his inability to fix his attention on the cards. A woman had a "sinking spell." One young man, who experienced a bolt of fire shooting through his brain, suffered from "brain fever" for three weeks (compare with "brain fever" of Dostoievski's novels).

From these descriptions, very inadequate in comparison with the description of the more remote results, one can deduce that in general the psycholeptic episode is followed immediately by a period of relative confusion, with decreased grasp of the situation, but not amounting

to disorientation in any of the cases forming the basis of this study. Less often the patient reacts to the attack with panic. One young woman, who suddenly felt one half of her brain snap and be displaced backward into the posterior portion of the skull, found herself some hours later tense and frightened and holding tightly to the bed to keep from screaming. Every one of these patients continued doing what he had been doing with an immediate sense of decrease of efficiency, leading to abandonment of the activity. In the first case mentioned, this came the following day; in the others, some days or weeks later. This fact is important and will be referred to later.

REMOTE SEQUELAE OF THE ATTACK

The more remote results of the episode vary widely with the evolution of the individual psychosis. There is commonly a feeling of depression, and one of these patients underwent a circumscribed depression. It was ushered in, following the psycholeptic attack, by worry over her physical status and over her sins of masturbation and the use of contraceptives. She made a good recovery nine months after the attack. A young man became deeply depressed from worry and preoccupation with a sodomy episode in youth; he showed marked depersonalization, with a hopeless, listless outlook, and with obsessive erotic thoughts. He made a complete recovery within one year after the attack. In another, anxiety attacks developed, forcing a reduction of activity, so that his work record in the ten years since the psycholeptic episode shows a notable slump; he took to alcohol, suffered marked depersonalization, and lately has become depressed over his wife's desertion because of his jealousy. Another young man suffered an exacerbation of anxiety attacks (which he had had for eight years), which then improved slightly with three years of psychoanalytic treatment, only to be replaced by extreme depersonalization. Four years after the attack, he is unable to manage outside the hospital because of anxiety attacks, alternating with periods of marked depersonalization, and a subjective sense of weakness and hopelessness, with suicidal ideas. There were transient bizarre ideas of being the Messiah or the greatest man in the world, with fanciful plans for conquering the world and fear of putting them into operation. Still another has been in and out of hospitals for four years because of alternating periods of "depression" and "elation," the latter brought about by ventilation and correction of some queer ideas about sex. There has been much preoccupation with the question of his "normalcy," with bizarre delusions about his eyes, face and hands, on a sexual basis, with a subjective sense of weakness that prevents him from doing any gainful work. Another patient, a very successful man, had to give up work

because of difficulty in concentration, accompanied by sudden severe head sensations of pressure and contracture. He developed many queer ideas about his somatic status, felt that he was becoming prematurely old sexually, and had a totally pessimistic and apathetic attitude toward himself and to the world in general. There were present the biologic features so common in depression, but no definite statement regarding depressive moods was ever obtained. He made no progress in sixteen months. Then suddenly he became "confused," felt that he was dead, and crept into bed with his mother. The next morning he awoke more cheerful and has made steady and rapid progress since.

One young woman has suffered a progressive deterioration of habits, with marked difficulty of concentration and attention, and three years later is on the verge of active auditory hallucinosis, with beginning paranoid projection, ambivalency, passivity feelings and hypochondriac concern. Another young woman, markedly depersonalized, has passed through periods of combativeness, irritability, anger, sadness and fear to a state of sullen mutism, sometimes with childish monosyllabic requests, refusing food, and with somatic delusions of her face being changed and her head shrunken. Still another young woman has suffered from obsessive erotic thoughts, self-recrimination, with marked feelings of unreality and recurrent states of panic, all in a strongly affective setting. Six years after the episode, and after eight months of hospitalization, she shows great improvement.

From these brief summaries it is evident that the psychosis follows no set course. Depression (not necessarily in the form of the circumscribed attack), apathy, hopelessness, obsessive thoughts and morbid ruminations, feelings of weakness, bizarre somatic delusions, paranoid projections, ambivalency, passivity feelings of the frankly schizophrenic development and depersonalization are commonly seen. In almost all cases the patients point to some "change" that has come over them since the attack. It is striking that depersonalization and feelings of unreality—"les sentiments du vide" of Janet—are perhaps the most constant features of this change.

One patient complained bitterly of having no feelings, of being completely devoid of all the sentiments that actuate normal people, and of having no sense of responsibility or of duty to himself or to others, no sense of pleasure, pain or anticipation. He felt that he was leading a vegetable existence. With this there was a sense of weakness. It is remarkable that depersonalization should be found side by side with anxiety attacks in the same patient. This patient, who had suffered from anxiety attacks for eight years underwent an extended psychoanalysis, during which his attacks diminished in severity. Finally they came infrequently, but there developed simultaneously extreme deper-

sonalization. Of the change the patient said: "I began to feel that in giving up my neurosis (i. e., the attacks) I had lost my life—my heritage." He welcomed the occasional return of the anxiety attack as evidence that he could "feel." This patient was unusually voluble in expressing his lack of feelings, but even the more inarticulate patients complained of a "change" in the same direction—of uselessness, lassitude and hopelessness, and of having no incentive either to live or to die. All the patients with this symptom dated it from the psycholeptic episode.

ANTECEDENTS OF THE ATTACK

The let-down, depressed, empty feeling is all the more notable because it stands in striking contrast to the emotional state preceding the attack. Moreover, in a study of these antecedents of the attack one arrives at the crucial part of the inquiry. The initial story given by the patient may or may not give a hint as to the presence of trouble prior to the attack. But a careful review of the history will in every case show two important facts: 1. There is always a story of mounting tension over a longer or shorter period preceding the attack. This tension is expressed as nervousness, depression (with its biologic features of loss of sleep, appetite, weight and sex desire, and constipation), restlessness and dissatisfaction. It results from unhappiness, worry, remorse, boredom and fatigue (from illness and overwork). The story may go back for years. The frequency with which preoccupation with sexual topics is found to be the basis of this mounting tension is natural and will be referred to later in a discussion of the personalities of the patients. The causes of the intensification of the tension immediately preceding the attack can always be found. For example, one patient, who four years before had had a sodomy episode in an attempt to gain the experience of the sexual act without harming any one, had suffered pangs of conscience since, but had been able to push the experience into the background with little effort. Then he was transferred to another city, away from home. He began to be concerned for his mother's happiness, for he knew his father was a drunkard and a "rounder." Vague plans for killing the father cropped up in his mind, plans that he realized would never be carried out. He felt that he should never marry because of his sin and in order to care for his mother, but vaguely wanted to marry, too. On the new job, life was all work and no play. There were too few social contacts. He was dissatisfied with his progress. Suddenly, while dining with a young woman, for whom he entertained a certain affection, he wondered: "What would she think if she knew the truth about me?" And in this situation, which was becoming increasingly difficult from these several sources of worry, the psycholeptic attack occurred.

2. There seems always to be an inadequate appreciation of this tension on the part of the patient. The appreciation may be in retrospect only, or he may have been somehow aware of it at the time. In any case, it is significant that the patient never makes any adequate attempt to change the factors causing the tension. There seems to be the general feeling that something is wrong, but that something is poorly understood and hence poorly combated. The particular straw that breaks the camel's back seems to have no significance in itself. As one goes over the history, carefully reconstructing the course of the illness, one cannot but be impressed with the many facts that should have been ample warning to the patient that trouble was in store for him, and as much by his utter inability to observe and act on these warnings. This apathetic, futile attitude toward the facts of his own illness preceding the psycholeptic attack persists even after the attack. The patient, in spite of the great change that has come over him, even in the period of confusion, tries to carry on in the same manner and in the same circumstances as before, and quits only when he finds it impossible to go on because of difficulties in concentration, depression, head sensations and the many other phenomena of the fully developed psychosis.[11]

The psycholeptic attack then comes as the first warning powerful enough through its own dramatic qualities to force a change from the course producing the tension. It is no mere signal pointing out danger, but a mighty power compelling a change of itself. According to the patient, it is this that produces the lingering results that finally make him seek medical help.

The patient is, in a sense, saved from the tension state by the timely intervention of the episode and the subsequent development of the full-fledged psychosis. It is this peculiar force of the attack, however, that proves the main obstacle to treatment. The patient may become so insistent that the attack is the etiologic factor in the illness as to be unable to accept it at its proper relative value.

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11. Pierre Janet wrote (History of Psychology in Autobiography, edited by Carl Murchison, Worcester, Mass., Clark University Press, 1930, p. 133): "I must mention a whole new study which has scarcely begun and which has as its object not only this psychological energy, but also the relationship between this energy and tension. I have approached part of this study in examining the phenomena of discharge which plays an essential part in convulsive attacks and in the *crises of psycholepsy*. Probably in normal life, among well-balanced individuals, a certain proportion must be maintained between disposable energy and tension, and it is not good to combine great energy with feeble tension or inversely to seek to maintain high tension with insufficient energy; the result is always agitation, insufficiency, and disorder. The most useful psychology of the future will be a practical psychology of conduct which will at the same time be dynamic and will study the physiological production of energy and its distribution."

SUBJECTIVE EVALUATION OF THE ATTACK

What does the psycholeptic episode mean to the patient? This question deserves some consideration, as on its answer depends to some extent the therapeutic approach. Not one of the patients forming the basis of this study was able without help to look on the experience with any insight. It is considered as something mysterious which is beyond understanding. This is, in part at least, due to the authority which the experience derives from its suddenness and its vividness. One woman said: "This is more than a depression. Something else happened, something supernatural. I feel as if I had lost my soul." One young girl said: "It's like a cracked plate—you can't fix a cracked plate." One young man did not know *what* hit him, but considered the experience as a punishment from God for his sins. It is probable, however, that the psycholeptic episode derives its greatest significance for the patient from the fact of its reference to the head. Something happening to the head (brain) must carry a meaning of enormous value to one who is in trouble mentally with partial appreciation of the fact. None of these patients showed any actual fear of losing his mind before the attack, although fear of insanity was noted later. The after-effects, especially the "change" in the direction of depersonalization, can only bolster the conviction that something really did happen to the brain. I have seen one woman, essentially depressed, but with many activities of a self-protective character, who only feared that something would snap in her head.

ORGANIC COMPONENTS OF THE ATTACK

At this point it should be said that nothing whatever is known of the organic components of the psycholeptic attack. The subjective sensations have been described, but no observations of the actual attack are available. This is no doubt due to the fact that the psycholeptic attack usually comes but once, suddenly and without warning. There is no constant biologic picture to be found in patients after the attack, although depressive features are common. These can generally be traced back to a time preceding the attack. In this lack of information, the psycholeptic attack stands in contrast to other episodic psychobiologic experiences with a different reference. The physical components of the anxiety attack, the hysterical seizure and the epileptic convulsion are, of course, well known.

OBJECTIVE INTERPRETATION OF THE ATTACK

It is interesting that all these episodic psychobiologic experiences serve the same function, namely, the diminution of tension (even to coma). They are all only climaxes. This fact is not always appre-

ciated by the patient. Only one of the patients with a psycholeptic attack spoke of the tension leaving him immediately after the attack. On the other hand, the epileptic sometimes welcomes the attack because of the conscious diminution of tension that it brings.[12]

It is this reference to the head (brain) that gives to the psycholeptic episode a more serious prognostic value than to the anxiety attack, for instance, in which the reference is mainly to the heart. However, anxiety attacks with fear of losing the mind are not uncommon, and one patient in a first anxiety attack became unconscious following a "stroke." Such an example serves again to point out the similarity of the two types of seizures. This patient was able to accept the completely functional nature of the "stroke," and his insistence was on the heart symptoms. One can say from the comparison that anxiety attacks with fear of losing the mind indicate a more serious involvement of the personality, in the psychotic development, than the simple anxiety attack or the anxiety attack with fear of death.

The psycholeptic attack may be considered the manifestation at the highest psychobiologic level of a sudden realization of insecurity on the part of the patient. In this respect, it bears again a certain relationship to the anxiety attack, in which the overt activity is generally confined to a lower integrative level. It has also in common with panic this basis of insecurity. It has already been pointed out that panic sometimes follows close on the heels of the psycholeptic attack. When it is remembered that panic is a phenomenon of aggression, the rarity of its appearance here is noteworthy and points to certain personality traits that will be discussed later.

Why does a psycholeptic attack develop in one patient and an anxiety attack, for instance, in another. This question involves what is back of Freud's phrase, the "choice of the neurosis." The answer

12. John T. MacCurdy (Diagnostic Significance of Sensory Aurae in Epilepsy, Brit. J. M. Psychol. **10**:38, 1930) reported the case of an epileptic as follows: "J. H. S. is now forty-eight. When twenty years of age he attended an epileptic in a fit, who 'spat between his eyes.' The patient was much frightened and had his first epileptic seizure half an hour later. His aura now is what he speaks of as a 'fright,' which comes like a blow which someone strikes him on the back of the head. He remarks that it is not a painful but a weak feeling. This sensation runs down the spine, but goes particularly to the eyes where it stays. When there, if he can take a deep breath and not get frightened, he can prevent the seizure. When told that he could not have caught epilepsy from the saliva of an epileptic he replied: 'I can't say as to that—as to that I don't know. But it sticks in my mind that it was that fright that brought on these fits.' He was manifestly incapable of getting rid of the idea that there was an infection, for this argument was repeated several times. Finally he said: 'That's a hard thing to beat. It's the thought I had from the first minute, and it seems I can't get rid of it.' He admits much encouragement, however, from his ability to hold the spells off."

PERSONALITY FACTORS

to this question is not to be found in isolated facts revealed by an examination of the antecedents of the attack. For in all types of attacks are to be found the same things—strife, dissatisfaction, boredom, morbid preoccupation, remorse, fatigue, insecurity—all leading to tension. Neither is the answer to be found in body types alone or other physical considerations (as far as is now known), nor in a study of the mental endowment and heredity factors.

The answer to this question is to be found only in a study of the actual personalities of the patients. In what kind of personality does the psycholeptic attack develop? An examination of the life histories of the patients forming the basis of this study has shown in almost every case a definitely egotropic, "shut-in" tendency, a wondering, perplexed, brooding personality, with a disposition to work out its problems unassisted, through sensitiveness, timidity or an innate inability to socialize itself, and without the feeling of necessity for checking up on the dominant ideas. The disposition of these people to go their own way is seen long before the psychotic development. This tendency becomes much plainer as the events of the psychosis unfold, and is seen in the apathy and the futile attempts to extricate themselves from the situations producing the tension, and in the remarkable lack of insight, even in retrospect, for the illness. One who has always lived his own life unassisted can scarcely be expected to seek help from others when trouble arrives. This blundering, groping, vague, unguided activity has its counterpart in the wondering, frightened or apathetic attitude toward the attack, and in the final feeling of hopelessness, that "something has happened to me now" feeling. Even in a patient with such definitely topical worries as the young man preoccupied with an experience of sodomy, producing tension leading up to the attack, there was no disposition to check up on these ideas by inquiry among others. This patient, as a corollary to his original "sin," a few weeks later, on hearing the "unpardonable sin" mentioned by a minister, immediately took that responsibility on himself. His statement of the fact is interesting. He felt that the experience of sodomy was a sin against nature, and as God was nature, his sin was a sin against God. Inquiry showed that, while he was an active church worker, he did not know the biblical statement relative to the unpardonable sin and had shown no disposition to inquire of the minister or others or to read the Bible itself to verify the facts. He accepted his sin and incorporated it into his vague, purposeless thinking.

Occasionally, the patient may make a belated attempt to reestablish the sense of security that has been shattered by the psycholeptic episode.

The following case will illustrate one mechanism. A young schizophrenic girl, in a setting of panic, suffered a feeling of the entire spinal column and head being split open—as if with a "zipper." At this time, the Holy Spirit left her, and for the first time in her life she enjoyed erotic sensations. The two halves of the body seemed different. The rift in the spine and head healed imperfectly thereafter, but finally the healing process was completed some time later, and the Holy Spirit returned to her through an ecstatic experience. This experience is much more complicated than the ordinary type of psycholeptic attack, and the symbolism unusually vivid. The dissociation into the somesthetic and the "spiritual" is interesting and served to indicate much of the catathymic material underlying the psychosis. The aggressive attempt of the personality to heal the rift through an ecstatic experience is noteworthy and points to ecstasy as holding much in common with the psycholeptic attack.[13]

The frequency of the sexual topic as the subject for the patient's preoccupation doubtless has many points of significance. From the standpoint of the personality of the patient it is significant as being one of those topics about which it is hard to be frankly inquiring and objective. For the person who is habitually reticent, timid and sensitive it presents a real difficulty. One patient (a Catholic) was worried over masturbation and the use of contraceptives. One young man, anxious to return home from France after the armistice, was worried over the possibility of a recurrence of gonorrhea, its detection and his detention in France. A young man, with strict ideas of honor, became dissatisfied with his fiancée, broke with her, and became engaged to another more to his fancy. He became much disturbed by the feeling that he had wronged the first girl, and the day after his engagement to the second the psycholeptic episode occurred. This man, apparently very successful in his work, which demanded meeting the public, had shown a complete inability to socialize any but his business notions and held to a queer lot of pseudoscientific ideas, especially about his sexual decline, with a tenacity that was truly remarkable. Another young man felt that he "never knew what it was all about," thought intercourse necessary to "grow up," became elated after the first experience,

13. Maudsley (footnote 1, pp. 318-319, footnote: Psycholepsy. "A term one may, perhaps, propose for use as fairly denominating a class of phenomena which call for further and more exact investigation. Several varieties might be formulated and described. For example: 1. Psycholepsy: a. Theological illumination or ecstasy. b. Metaphysical intuition or ecstasy. c. Catalepsy and its allied trances. d. Fanatical transport of enthusiasm or of fury. e. Frenzy of epidemic emotion. f. Fascination of fear. g. Ecstasy of gross brain disease."

and then when he could not repeat the experience, owing to circumstances, became preoccupied and tense. Four years later, he is still much preoccupied with sexual ideas, many of them queer and bizarre. It is interesting that the patient previously mentioned, who was afraid something would snap in her head, was preoccupied and worried over masturbation before coming to the hospital and a homosexual attachment made in the hospital. In some cases, the sex conflict is not obtainable, but, largely for the reason mentioned, it has a higher frequency than any other single topic.

The shut-in personality, as already described, is less well seen in patients presenting both the psycholeptic episode and anxiety attacks. There was a tendency for these patients to make a certain degree of progress, and then to slump when confronted with the necessity of facing the world, of living and working outside the hospital. So, in general, they exhibited the phenomena of Janet's lower psychologic tension and their condition would doubtless have been included under his "psychasthénie." "Psychopathic personality" seems a better descriptive term to apply to these anxious, hypochrondriac, depersonalized, fantastically day-dreaming persons.

Janet viewed the phenomena of lowered psychologic tension as the essential features of his "psychasthénie." The case material that he presented included a great many cases that one might well include in other categories of mental disease. Others look on the psycholeptic attack as a symptom of the schizophrenic development. From the cases presented here, the episode has been seen in all types of reactions —in cases that may be considered fundamentally as depression (topical or endogenous), in unstable (psychopathic) personalities, in the anxiety neuroses and in frankly schizophrenic developments. In most, if not all, of the cases there is a certain parergastic coloring. Even the cases that seem fundamentally depressive show features that are outside the uncomplicated picture of depression. These parergastic features are the bizarre ideas, the vagueness, the indecisiveness, the somatic delusions and paranoid projections. There is rarely ever a true passivity feeling toward the attack on the part of the patient. This parergastic coloring then is chargeable to the egotropic personality of the patient, rather than to the psycholeptic episode as part of the symptomatology.

RELATION TO RELIGIOUS CONVERSION AND PARANOIAC INTUITION

The psycholeptic episode has been referred to by Adolf Meyer as a sort of "anti-conversion" experience. The comparison is useful in

many points. In religious conversion, according to William James,[14] two factors are necessary: (1) concern and worry over guilt and sin and (2) a positive ideal toward which one struggles. In most cases, the former factor predominates almost to the total exclusion of the latter. Whether the conversion is gradual or sudden depends on the rate of self-surrender. In every case, however gradual or rapid, this self-surrender would seem to be indispensable. The striking feature —and the one that contrasts with the psycholeptic episode—is the self-surrender in the full faith of deliverance by Omniscience. No such comfort is found in the psycholeptic attack. In this, the patient surrenders with a firm belief in his unhappy doom. It is worth noting that the patient who suffers a psycholeptic attack is certainly no more concerned over his misdemeanors than the person seeking conversion. He is not sustained, however, in the moment of the attack by the "positive ideal."

According to James, there are three effects of conversion. These may be compared point by point with the changes that follow the psycholeptic attack: 1. Tension as an expression of worry is gone, or if worry persists, it carries no charge. There is a resignedness about this which somehow compares with the "willingness to be" of the convert. 2. There is a perception of truths hitherto unperceived—one has only to remember the young man with the experience of sodomy who rationalized his psycholeptic episode as punishment from God. The truth of this assumption seemed unquestionable to him. 3. Feelings of unreality are present. The most striking comparison is possible here; even the most trivial items of everyday existence are altered for the patient.

James spoke of "counter-conversion" to denote the transition from orthodoxy to infidelity. In conversion and in counter-conversion, the somesthetic reference to the head seems to be absent.

The psycholeptic attack also seems to have something in common with the "intuition" of the paranoiac. This common property is the authority of experience, which in turn comes from its vividness and suddenness, but in part from the patient's egotropic willingness to accept the experience. In patients with a psycholeptic attack, this willingness is a personality trait, in keeping with their habitual reaction, their unsocialized thinking.

PSYCHOLEPTOID ATTACKS

Patients occasionally report incidents that in some respects resemble the psycholeptic attack described, but that deviate in some important essential. The following examples will illustrate some types.

14. James, William: The Varieties of Religious Experience, New York, Longmans, Green & Company, 1915.

An elderly man suffered from sensations of dizziness with sudden confusion incident to a minor cerebral accident. Shortly thereafter a full-fledged obsessive compulsive state of tension with depression developed, which has persisted for six years. He is unable to believe that his present state has any resemblance to his condition before the cerebral hemorrhage—in reality only an exaggeration. He blames the accident for it and speaks constantly of something wrong with the brain. This case shows how retrospective misinterpretation of a common biologic event may create a situation which resembles somewhat that in the group of cases previously presented.

Snapping of the head has also been observed [15] in paranoid confusional states with depression and in organic disease of the brain (tumor), which in the total picture seemed to hold no significance for the patient. In another paranoid delusional development in an affective setting, one of the three principal delusions disappeared (according to the patient) after a snap in the head. In a feebleminded boy with manic-depressive psychosis, the transition from the depressed to the hypomanic phase was with a snap in the head. It is impossible to evaluate these episodes.

I have seen only one normal, healthy person who had experienced anything resembling the psycholeptic attack. This man, a psychiatrist, stated that for several years, at intervals of from three to six months, he experiences a sudden low hum in the ears and that this is almost immediately followed by a tremendous sensation as of an anvil being struck a heavy blow. He described the experience as 75 per cent auditory and 25 per cent concussion. The blow seems to traverse the skull in the intertemporal region. The episode usually comes when he is perfectly quiet, often when he is in bed before going to sleep, and is not preceded by any tension of which he is aware, nor is it followed by a feeling of unreality or other sense of change. He is generally startled by the event. He offers no explanation for the experience.

THERAPY

The therapy, as far as the psycholeptic episode is concerned, is the same no matter what the psychotic picture. It aims to socialize, to minimize and to rationalize the experience to the patient. This is done best by retracing the events leading up to the attack and pointing out the attack then as the climax only to a rather long maladjustment. The effectiveness of this approach is generally aided by the poor appreciation of these facts by the patient. It is often during this rationalization that there comes to him the first clear realization that he was in trouble

15. Unreported cases from the Henry Phipps Psychiatric Clinic, the Johns Hopkins Hospital.

beforehand. It then is easier to connect his present sad state with these events, giving them a rational foundation in place of their supernatural origin through the psycholeptic episode. It is an attempt to improve the insight. The method is especially valuable in cases showing depression as the fundamental picture; less so the more prominent become the parergastic features. In this attempt to minimize and rationalize the experience one must not forget to point out the lifelong peculiar personality traits, which have allowed the facts of the whole illness, not only the episode, to go unquestioned, unchecked by inquiry from others.

BLOOD LIPASE, DIASTASE AND ESTERASE IN MULTIPLE SCLEROSIS

A POSSIBLE INDEX OF LIVER DYSFUNCTION *

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We previously made a preliminary report [1] confirming the observations of Brickner [2] on a lipolytic substance in the blood serum of patients with multiple sclerosis. At that time we proposed that rather than being an etiologic factor, as Brickner suggested, the presence of this enzyme in the blood might be an indication of functional insufficiency of the liver or pancreas. We have reported on an abnormal lipase in the blood in experimental damage [3] of the pancreas or liver and in patients with hepatic disease.[1] Recently we have shown that the blood diastase is also increased following experimental injury of the liver,[4] and have suggested that normally pancreatic lipase and diastase are absorbed from the lumen of the intestine, but are removed (lipase completely and diastase partially) from the portal blood by the liver. In this connection it is important to bear in mind the distinction between the esterase, which attacks such substrates as ethyl butyrate and tributyrin, and which is present in blood and all tissues studied except cerebrospinal fluid, and the lipase that is present in largest amount in the pancreas and is not normally detectable in the blood.[5] The enzyme that Brickner studied should strictly be termed a lecithinase, since the only specific substrate on which he demonstrated its activity is lecithin. Lipase (or steapsin) acting on the triglycerides of the higher fatty acids is usually differentiated from lecithinase,[6] but it is possible that they may be the same enzyme.

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1. Crandall, L. A., Jr., and Cherry, I. S.: Proc. Soc. Exper. Biol. & Med. **28**: 572, 1931.

2. Brickner, R. M.: Bull. Neurol. Inst., New York **1**:105, 1931.

3. Crandall, L. A., Jr., and Cherry, I. S.: Proc. Soc. Exper. Biol. & Med. **28**:570, 1931.

4. Crandall, L. A., Jr., and Cherry, I. S.: Am. J. Physiol. **97**:515, 1931.

5. Cherry, I. S., and Crandall, L. A., Jr.: Am. J. Physiol., to be published.

6. Oppenheimer, C.: Die Fermente und ihre Wirkungen, ed. 5, Leipzig, F. C. W. Vogel, 1925.

In the present study, we have extended our observations on a lipase that is present in the blood of patients with multiple sclerosis, liver disease and pancreatic disease and in dogs with experimental damage of the pancreas or liver. If this enzyme were of pancreatic origin, it seemed likely that it would be accompanied by other enzymes from the pancreas; we have therefore extended our studies to include diastase. The esterase of the blood has also been determined in many cases.

METHODS

The technic used for the determination of lipase and esterase has been described elsewhere.[5] Titration methods were used for both enzymes. In the case of lipase a very fine and stable emulsion of olive oil, preserved by the addition of sodium benzoate, was used as the substrate. The substrate for esterase was absolute ethyl butyrate. In both cases a constant initial p_H was insured by the addition of a phosphate buffer. The results were expressed as cubic centimeters of twentieth-normal sodium hydroxide required to neutralize the fatty acid set free from 2 cc. of a 50 per cent olive oil emulsion, or from 1 cc. of ethyl butyrate, by 1 cc. of serum during a twenty-four hour incubation at 40 C.

For the determination of diastase, the method described by Davison[7] was adapted for use with blood serum. The method depends on changes in viscosity in a starch solution when the starch is hydrolyzed by diastase. In our hands the method has been accurate within plus or minus 5 per cent. To adapt the method to serum it was necessary to use saline solution in making up the substrate, since if distilled water is used the serum proteins will precipitate and clog the viscosimeter. We made up the starch solution as follows: 150 cc. of 0.9 per cent sodium chloride was added to 2 cc. third-molar phosphate buffer adjusted to a p_H of 7 and 50 cc. distilled water. To this solution was added 3.5 Gm. of Lintner's soluble starch (many so-called soluble starches contain large percentages of dextrin; we have found Merck's preparation to be satisfactory), and the mixture was brought to a boil over a flame. The flask was then stoppered with gauze, and autoclaved for fifteen minutes at a pressure of 20 pounds. The resulting solution was filtered at least twice through the same filter paper to remove all suspended particles.

We expressed our results in terms of units as defined by Davison.[7] It is unfortunate that Elman, Arneson and Graham,[8] who also employed this method for blood disastase, departed from the definition of the unit as originally given. Davison's unit, used by us, is that amount of diastase which will change the viscosity of 10 cc. of a starch substrate, such as that already described, by 20 per cent in one hour at 34 C.

Serum was consistently employed as the source of enzymes rather than plasma, because anticoagulants tend to interfere with enzymatic activity. Determinations of lipase were always made within six hours after the blood was obtained, although the serum retains a uniform lipolytic activity for at least twenty-four hours. Diastase appeared to be even more stable in serum, remaining constant for forty-

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7. Davison, W. C.: Bull. Johns Hopkins Hosp. **37**:281, 1925.

8. Elman, R.; Arneson, N., and Graham, E. A.: Value of Blood Amylase Estimations in Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec.) 1929. Stocks, P.: Quart. J. Med. **9**:216, 1915. Wakefield, E. G.; McCaughan, J. M., and McVicar, C. S.: Amylase in Blood in Subacute and in Chronic Pancreatic Diseases, Arch. Int. Med. **45**:473 (March) 1930.

eight hours; however, diastase determinations were always made within twenty-four hours. Most of the patients with multiple sclerosis were obtained from the Oak Forest Infirmary. In every case the diagnosis of multiple sclerosis was confirmed by at least two neurologists. Control patients were obtained chiefly from the Northwestern University Dispensary. Tests for the presence of an abnormal olive oil-splitting lipase were made 45 times in 27 cases of multiple sclerosis; many of these were run in duplicate. One sample of serum from each of 131 controls and 10 cases of liver disease was studied. In most cases the diagnosis in the control serum was not known until after the lipase determinations had been made. The controls were unselected and were studied in the order of the admission of the patients to the dispensary, except that cases of liver disease were excluded from the control series and classified separately. Because of the possible influence of environment, especially diet, on the blood enzymes, a separate series of controls was obtained from the Oak Forest Infirmary.

TABLE 1.—*Diastase, Lipase and Esterase in Multiple Sclerosis*

Case	Diastase Units	Lipase Titer, Cc. N/20 NaOH	Esterase Titer, Cc. N/20 NaOH
1*	...	0.3	
	1.9	0.1	
2*	...	0.3	2.5
3*	...	0.6	2.8
	1.3	0.1	
	1.3	0.1	
4*	...	0.5	2.4
5*	...	0.7	2.6
	1.0	0.3	
6*	...	0.5	2.4
7*	...	0.5	2.2
8*	...	0.6	2.6
	1.7	0.0	
	1.9	0.2	
9*	...	0.5	2.7
10*	...	0.1	
	1.0	0.0	2.6
	1.0	0.0	
	1.1	0.1	
11*	...	0.5	2.9
	1.3	0.0	
	1.5	0.4	
	1.6	0.0	
12*	...	0.4	2.7
13	1.9	0.3	
14	1.5	0.0	
15*	1.0	0.4	
	1.1	0.2	
16*	2.6	0.2	
	2.2	0.6	
17*	2.1	0.0	
	1.8	0.0	
18*	1.5	0.1	
19*	1.6	0.0	
	1.8	0.2	
20*	1.1	0.1	
	0.9	0.3	
21*	1.2	0.1	
	1.3	0.2	
22*	1.6	0.2	
23*	3.1	0.4	
	2.8	0.5	
24*	1.2	0.3	
25	1.0	0.0	
26	1.6	0.0	
27	1.8	0.6	

* Patients from Oak Forest Infirmary.

A case was considered as showing a positive lipase if at any time the lipase value was found to be 0.2 cc. or greater.

Diastase determinations were made 34 times in 21 cases of multiple sclerosis and once in each of 36 controls. Because of possible accidental contamination with saliva, all serums showing high diastase were run in duplicate. The values are given in tables 1, 4 and 6. The figure of 1.5 units was selected as the upper limit of normal. The incidence of diastase values higher than this in the control series (8.3 per cent) is close to that of the incidence of positive lipase observations in the controls (7.6 per cent). Because of the close correspondence of repeated diastase determinations on the same patient (table 1), the average of all determinations was taken in summarizing the data in table 6.

TABLE 2.—*Lipase Values in 114 Unselected Controls*

Case	Diagnosis	Lipase Titer, Cc. N/20 NaOH
95 cases	.....	0.0
11 cases	.....	0.1
107	Astigmatism.....	0.5
108	Psoriasis.....	0.3
109	Cataract.....	0.4
110	Arteriosclerosis.....	0.5
111	Arthritis.....	0.3
112	Birth palsy.....	0.2
113	Cerebellar medulloblastoma.....	0.3
114	Cardiac decompensation.....	0.2

TABLE 3.—*Lipase Values in Selected Controls with Disease of the Central Nervous System*

Case	Diagnosis	Lipase Titer, Cc. N/20 NaOH
1	Chronic encephalitis.....	0.2
2	Chronic encephalitis.....	0.1
3	Chronic encephalitis.....	0.0
4	Dementia paralytica.....	0.0
5	Dementia paralytica.....	0.0
6	Dementia paralytica.....	0.0
7	Dementia paralytica.....	0.0
8*	Hemiplegia, marked cachexia.....	0.0
9*	Hemiplegia.....	0.0
10*	Hemiplegia.....	0.0
11*	Traumatic lesion of cauda equina.....	0.0
12*	Hemiplegia.....	0.0
13*	Hemiplegia (syphilis ?).....	0.2
14*	Hemiplegia.....	0.0
15*	Hemiplegia.....	0.1
16*	Hemiplegia.....	0.0
17*	Hemiplegia.....	0.0

* Patients from Oak Forest Infirmary.

TABLE 4.—*Lipase and Diastase Values in Cases of Liver Disease*

Case	Diagnosis	Lipase Titer, Cc. N/20 NaOH	Diastase Units
1	Cancer of biliary tract.....	0.6	
2	Cirrhosis.....	0.0	
3	Common duct stone.....	0.5	
4	Cirrhosis.....	0.5	1.5
5	Alcoholic cirrhosis.....	0.9	2.0
6	Catarrhal jaundice.....	0.2	2.1
7	Inflammatory jaundice.....	0.4	2.6
8	Toxic hepatitis.....	0.3	2.2
9	Obstructive jaundice.....	0.5	2.0
10	Obstructive jaundice.....	0.1	1.2
11	Chronic cholecystitis.....	...	1.9

RESULTS

Tables 1 to 7 include all data and are self-explanatory. Our previous discovery of a high incidence of a lipase in patients with multiple sclerosis rarely present in normal persons is confirmed, 78 per cent of those with multiple sclerosis showing such an enzyme as against 7.6 per cent of the controls. The incidence of this lipase in our cases of involvement of the liver was 80 per cent.

TABLE 5.—*Summary of Lipase Studies*

Diagnosis	Number of Patients	With Lipase of 0.2 or Greater	
		Number	Per Cent
Multiple sclerosis	27	21	78
Liver disease	10	8	80
Controls with central nervous system disease	17	2	11.8
All controls	131	10	7.6

TABLE 6.—*Diastase Values in Thirty-Six Control Cases and Twenty-One Cases of Multiple Sclerosis*

Number of Patients	Diagnosis	Average Diastase Value in Units	Above 1.5 Units	
			Number	Per Cent
19	Unselected controls from dispensary	1.2	2	10.5
3	Chronic encephalitis	1.37	0	0.0
4	Dementia paralytica	1.1	0	0.0
10	Controls from Oak Forest Infirmary chiefly hemiplegias	1.2	1	10.0
21	Multiple sclerosis (table 1)	1.53	10	47.6
36	All controls	1.27	3	8.3
8	Liver disease	1.8	6	75.0

TABLE 7.—*Blood Esterase in Seventy-Nine Controls and Eleven Patients with Multiple Sclerosis*

	Esterase in Cc. N/20 NaOH		
	Average	Maximum	Minimum
Controls	2.2	3.1	1.0
Multiple sclerosis	2.6	2.9	2.0

All values on the blood esterase in cases of multiple sclerosis were within normal limits. The fact that the average for patients with multiple sclerosis is slightly higher than that of the controls is without significance, especially since we commonly found low esterase values in

cachectic controls, while the patients with multiple sclerosis were almost without exception well nourished.

The incidence of abnormally high diastase values in multiple sclerosis (47.6 per cent) was not as high as that of positive lipases, but greatly exceeded that of the control series (8.3 per cent). This enzyme also was increased in the majority of patients with involvement of the liver (75 per cent).

COMMENT

Enzymes resembling pancreatic lipase and diastase unquestionably occur in the serums of patients with multiple sclerosis in larger amounts, on the average, than in the serums of patients with other complaints, exclusive of diseases of the liver or pancreas. Since only two cases of pancreatic disease were available (both cancer of the head of the pancreas), they were not included in the tables, but both showed positive lipase values; diastase was not studied in these cases, but others have shown greatly increased diastase (amylase) value in such conditions.[8]

The interpretation of these facts is difficult, and a positive statement as to their significance is at present impossible. In view of the myelinolytic type of change that occurs in the central nervous system in multiple sclerosis, the suggestion that the lipase might be responsible is logical. But it is difficult to reconcile this hypothesis with the demonstrated occurrence of the lipase in patients with involvement of the liver or pancreas. The longest time during which we have followed any case of liver disease is one month. The high incidence of the lipase in these cases suggests, however, that it is present over long periods. It also occurs in experimental injury of the liver or pancreas. We have followed several dogs with Eck fistulas for more than six months, and in these animals the lipase is more consistently present than in cases of multiple sclerosis. In such dogs the lipase usually disappears on starvation, which we believe bears out our hypothesis that its presence signifies failure of the liver to remove it from the portal blood after its absorption from the intestine. If this is true, it is not surprising that it should be only periodically present both in patients and in experimental animals. In dogs with complete obstruction to the outflow of pancreatic juice (excision of the body of the pancreas), we have observed lipase values much higher than those seen in any other clinical or experimental conditions, the average value for the first few postoperative days being about 5 cc. of twentieth-normal sodium hydroxide. The longest time that we have followed any such animal is fifty-two days; at the end of that time the lipase titer was 0.8 cc. twentieth-normal sodium hydroxide. In none of these animals have we observed any symptoms referable to the nervous system.

It is true that changes in the central nervous system are frequently observed in severe involvement of the liver,[9] but the changes are usually those of a diffuse parenchymatous degeneration. Matthews[10] has reported that dogs with an Eck fistula, chronically intoxicated with meat, may show a syndrome somewhat resembling that of multiple sclerosis, and one of us (Dr. Crandall) has observed various motor and sensory paralyses, as well as astasia, in such animals, although a neuropathologic study conducted by Dr. Weil has thus far shown nothing significant. It seems probable, however, that any lesions of the central nervous system that may occur secondary to injury of the liver depend on some factor other than the presence of this abnormal lipase.

Positive lipase and high diastase values are present not only in animals with an Eck fistula but also in dogs with complete obstruction of the common bile duct; Tomioka[11] has also reported increased diastase values in animals with various types of injury of the liver and in liver disease in man. Elman, Arneson and Graham[8] did not observe increased blood diastase values in liver disease without pancreatic involvement.

Whatever the mechanism may be by which increased amounts of these enzymes reach the blood stream, the fact remains that the only other conditions under which they are increased, both in the experimental animal and in man, are pathologic changes in the liver or pancreas. The values for both diastase and lipase found in pancreatic involvement are usually much higher than those that are found in multiple sclerosis, liver disease or experimental injury of the liver. Chevassut[12] has reported that decreased liver function is present in about 70 per cent of cases of multiple sclerosis. Unfortunately, the tests that she used are of doubtful value. However, our discovery of increased amounts of pancreatic enzymes in the serum may be confirmatory evidence. We believe that at present the best interpretation of the presence of abnormal amounts of lipase and diastase in the serum of patients with multiple sclerosis is that they are evidence of dysfunction of the liver.

CONCLUSION.

1. A lipase capable of splitting olive oil appeared in 78 per cent of the cases of multiple sclerosis, in 80 per cent of the cases of liver diseases and in 7.6 per cent of cases of other diseases.

9. Weltmann, O.: Wien. med. Wchnschr. **77**:831, 1927. Rapoport, B. I.: Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:473, 1930. Lapinsky, M.: Deutsche Ztschr. f. Nervenh. **97**:95, 1927.

10. Matthews, S. A.: Am. J. Physiol. **76**:219, 1926.

11. Tomioka, T.: Jap. J. Gastroenterol. **2**:254, 256, 1930.

12. Chevassut, K.: Aetiology of Disseminated Sclerosis, Lancet **1**:218 and 552, 1930.

2. Diastase values above what may be considered normal were found in 47.6 per cent of the cases of multiple sclerosis, in 75 per cent of the cases of liver disease and in 8.3 per cent of the controls.

3. Blood esterase (active on ethyl butyrate) showed no significant changes.

4. Animal experimentation bearing on the significance of these observations is discussed.

5. It is suggested that the best interpretation of the facts that can be made at the present is that they signify a functional disturbance of the liver in multiple sclerosis.

A SEROLOGIC STUDY OF MULTIPLE SCLEROSIS.*

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The present investigation includes three major problems. The first was an attempt to repeat the experiments of Chevassut [1] and of Purves-Stewart [2] and to demonstrate the presence of a filtrable virus as an etiologic factor in multiple sclerosis. The second was a repetition of work done previously by Brickner,[3] who tried to demonstrate the action of a myelolytic ferment in the plasmas of patients suffering from multiple sclerosis. At the same time, the observations were compared with the results of the lipase tests performed by Crandall [4] on our own patients in order to find out whether there was any correlation between the amount of lipase present and the degree of demyelinization of the spinal cord of rats. The third problem was an investigation of the inorganic phosphorus content of the serum of patients with multiple sclerosis, which was undertaken with the hope that it might shed light on the metabolism of phosphorus in multiple sclerosis in general, and at the same time indirectly on the metabolism of the phospholipids, the most important constituents of the myelin sheaths.

The results of the reinvestigation of Chevassut's work were disappointing. The conclusion was reached that the "spheres" that had been described and photographed were colloidal particles, submicrons precipitated in the mixture of agar broth, serum and spinal fluid, perhaps to a greater extent in the presence of "positive" spinal fluids containing globulin. The observations will be reported elsewhere.[5]

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* From the Institute of Neurology, Northwestern University Medical School.

1. Chevassut, K.: The Aetiology of Disseminated Sclerosis, Lancet **1**:552, 1930.

2. Purves-Stewart, James: A Specific Vaccine Treatment in Disseminated Sclerosis, Lancet **1**:560, 1930.

3. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930; Bull. Neurol. Inst. **1**:105 (Jan.) 1931.

4. Crandall, L. A., Jr., and Cherry, L. S.: Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis, Proc. Soc. Exper. Biol. & Med. **28**:572, 1931.

5. Weil, A.: The Etiology of Multiple Sclerosis, J. A. M. A. **97**:1587 (Nov. 28) 1931.

The sources of errors that have to be thought of in a laboratory research on multiple sclerosis are numerous. There is first to be considered the validity of the clinical diagnosis. The discovery of "spherules" by Purves-Stewart [2] in 93 per cent (176 of 189) of a group of cases diagnosed clinically as multiple sclerosis represents an optimum that can be expected to be verified on the autopsy table only if well advanced cases are selected. In collecting our own material from private and dispensary patients and inmates of Cook County and Wesley Memorial hospitals, the Oak Forest Infirmary, the Montefiore Hospital, New York, and the Wisconsin State Hospital, we accepted only those cases in which at least two neurologists had agreed on the diagnosis of multiple sclerosis. Furthermore, in accepting the rating of frequency of signs and symptoms of Sachs and Friedman [6] we expected at least five of the seven signs enumerated in table 1 to be present:

TABLE 1.—*Comparison of Frequency of Clinical Symptoms in Cases of Sachs and Friedman and in Twenty-Six of Our Cases*

	Sachs and Friedman, per Cent	26 Cases of Multiple Sclerosis, per Cent
1. Easy fatigue, weakness and stiffness of one or both upper or lower extremities culminating in spastic paraplegia with	81.7	100
(a) Increase of deep reflexes	90.0	100
(b) Positive Babinski sign	78.3	87
2. Nystagmus	70.0	81
3. Ataxic tremor of upper extremities	55.3	81
4. Marked diminution or loss of abdominal reflexes	83.7	92
5. Scanning speech or some form of dysarthria	36.0	58

Another difficulty was to decide whether or not we should include cases that had shown remissions lasting for years, presenting a stationary clinical picture. It was decided to accept only cases that presented a slowly progressive course. Furthermore, the group was confined to patients in whom the onset of the disease had occurred between the nineteenth and forty-second year of age, and who at the date of the examination were not older than 45.

The statistics collected by Wechsler [7] show that the onset of the disease in 70 to 75 per cent of all cases occurs between the ages of 20 and 40 years. Allison [8] collected 692 cases from the literature, and found that 80 per cent occurred between the ages of 20 and 40 years. Our own cases are compared with those of Wechsler, with those of Allison and with twenty-two cases of Schilder's disease from Gasul's review [9]

6. Sachs, B., and Friedman, E. D.: General Symptomatology of Multiple Sclerosis, New York, Association for Research in Nervous and Mental Diseases, 1921, vol. 2, p. 49.

7. Wechsler, I. S.: Statistics of Multiple Sclerosis, ibid., 1921, vol. 2, p. 32.

8. Allison, R. S.: Disseminated Sclerosis in North Wales, Brain **53**:391, 1931.

9. Gasul, B. M.: Schilder's Disease, Am. J. Dis. Child. **39**:595 (March) 1930

in which the onset was traced back to the ages of from 19 to 42 years (table 2).

The sex distribution in our twenty-six cases was: twenty men and six women. Nine were American born and seventeen European born (five Irish; two each, German, Italian, Lithuanian, Polish and Czechoslovak, and one each Hungarian and Swedish).

THE EFFECT OF SERUM OF PATIENTS WITH MULTIPLE SCLEROSIS ON THE SPINAL CORDS OF RATS

Three cubic centimeters of serum was incubated with a piece of the spinal cord of a rat (albino rat), approximately 5 mm. in length, and kept for twenty-four

TABLE 2.—*Age of Onset of Disease* *

	Age at Onset				
	19 to 30 Years		31 to 42 Years		
	Number	Per Cent	Number	Per Cent	City or Country
Multiple sclerosis, 26 cases, Chicago..	14	54	12	46	Chicago
Multiple sclerosis, 137 cases, Wechsler	65	47	72	53	New York
Multiple sclerosis, 47 cases Allison...	28	59	19	40	Northern Wales
Multiple sclerosis, 456 cases, Allison..	226	49	230	51	Switzerland..... 191
					United States... 185
					Northern Wales 47
					Germany..... 24
					Spain..... 9
Schilder's disease, 22 cases, Gasul....	10	45	12	55	

* Only those cases were selected from Wechsler's and Allison's material in which the disease began between the ages of 19 and 42 years.

TABLE 3.—*Comparison of Effect of Serum and Plasma of Patients with Multiple Sclerosis on Spinal Cords of Rats*

	Number of Cases			Per Cent			Brickner, per Cent				
Degree of Demyelinization	+	++	+++	+	++	+++	No. of Experiments	— to +	+	++	+++ and ++++
26 cases of multiple sclerosis...	9	8	9	35	30	35	42	0	5	21	74
7 normal persons.....	5	2	0	71	29	0	39	15	39	28	18
7 different diseases*.....	3	2	2	32	29	29					

* The seven cases of different diseases were: —, thrombotic softening of spinal cord following operation (one case); +, spastic paraplegia (one case) and otitis media (one case); ++, cerebrospinal syphilis (one case) and postoperative thrombotic softening of the spinal cord (one case); +++, hematomyelia (one case) and pontile hemorrhage (one case).

hours at 37 C. under as sterile conditions as possible. The spinal cord was then fixed in formaldehyde and embedded in a collodion preparation, and sections were stained by the Weil and Davenport methods and with cresyl violet.

The degree of damage done to the myelin sheaths was determined by the following grading in accordance with Brickner's[3] description: —, no marked changes; +, swelling of the myelin sheaths; ++, swelling of the myelin sheaths with general disarrangement and disorganization of their pattern and running together of myelin sheaths; +++, the same condition as in ++, with marked demyelinization, producing an outer slightly stained or unstained zone.

From a comparison of Brickner's tabulation with ours it is evident that he obtained a greater percentage of severely damaged spinal cords, both in the normal cases and in those of multiple sclerosis, than we did. This difference may be due to a different personal interpretation of the histologic pictures of the spinal cord sections or to the use of plasma instead of serum in Brickner's experiments. In sections stained for axons (Davenport method), marked swelling and distortion of the axis cylinders were seen in the areas that were affected in the myelin sheath stained sections. But the integrity of the axon was preserved. In sections stained with cresyl violet the peripheral zones showed a diminution or absence of glia nuclei.

TABLE 4.—*Lipase Content of Serums of Patients with Multiple Sclerosis Compared with the Action on the Spinal Cord of Rats and Inorganic Phosphorus Content of the Serum*

Case	Lipase*	Demyelinization	Inorganic Phosphorus Mg. per 100 Cc. of Serum
7	—	+	2.9
24	—	—	3.4
26	+	—	...
11	—	++	2.9
8	—	++	3.3
11	—	+++	2.3
4	+	+++	2.5
25	++	+++	3.2
30	++	+++	...
10	+++	—	3.2
20	+++	++	...
25	+++	++	3.2

* The lipase activity was determined by incubating serum with an olive oil emulsion and titration of the acid formed with twentieth normal sodium hydroxide. Lipase + = 0.2-0.3 cc. twentieth normal sodium hydroxide; ++ = 0.4-0.5 cc.; +++ = 0.6-0.7 cc.

From both sets of figures it seems, however, that quantitatively the serums and plasmas in cases of multiple sclerosis produce greater damage to the spinal cord of rats than do normal serums and plasmas. That this fact cannot be utilized for a differential diagnosis and does not have any bearing in itself on the etiology of multiple sclerosis is seen in the action of the serums of hospital patients, which show the same incidence of ++ and +++ damage as do the serums in cases of multiple sclerosis.

In order to decide whether the greater destructive action of multiple sclerosis serums was due to an increase in lipase, the results in a number of experiments were compared with those obtained by Crandall [4] in the same cases.

In eight of twelve experiments, demyelinization was ++ or +++ (67 per cent). In four of twelve experiments, demyelinization was +++ (33 per cent). In two of five cases with lipase ++ or +++,

the demyelinization was +++ (40 per cent). This compares with Crandall's figures of eleven of thirty-nine serums of patients with multiple sclerosis containing an amount of lipase of ++ or +++ (28 per cent). Table 4 demonstrates that no marked demyelinization of the spinal cord of rats is obtained in serums in which the titration value for lipase is less than 0.2 cc. of twentieth-normal sodium hydroxide. On the other hand, the damage to the spinal cord does not parallel the amount of lipase present, and in one case there was no destructive action despite a lipase content of +++.

In order to decide whether the changes that had been observed in the spinal cord of rats were produced by a lipase, as claimed by Brickner,[3] or whether some unknown cause might be responsible, the following series of experiments was done:

Glycerin extract of beef pancreas, which we obtained by the courtesy of Dr. Crandall, was incubated with rats' spinal cords for twenty-four hours at 37 C. In the dilution 1:80 it had a lipolytic action on olive oil of 9+ (1.8 cc. of twentieth-normal sodium hydroxide). The undiluted extract and the dilutions of 1:30, 1:60, and 1:80 were tested, a phosphate buffer solution with p_H 7.6 being used. As controls, the buffer solution and a lipase solution of the dilution, 1:30, which had been boiled for several minutes, were used.

The histologic pictures of the sections stained for myelin did not differ greatly in the experiments and in the controls. All of them resembled the picture that one is accustomed to see in the 0.85 per cent sodium chloride controls of the serum experiments; nothing indicated that the lipase had attacked and dissolved the myelin sheaths. There was no indication of any relation to the action of multiple sclerosis serum on rats' spinal cords (figs. 1 to 4).

THE DETERMINATION OF INORGANIC PHOSPHORUS IN SERUM

It is difficult to compare the data for serum phosphorus in publications prior to 1925 with our own results, because we used the methods of Fiske and Subbarow.[10] In more recent publications the average value for inorganic phosphorus in 100 cc. of serum is given as approximately from 3.8 to 3.9 mg., a value somewhat higher than the textbook figure of 3.7 obtained with earlier methods. In female patients, menstruation seems to play an important rôle in the phosphorus content of the serum, which is decreased in the premenstrual and increased in the postmenstrual period (Okey, Stewart and Greenwood[11] gave composite values in twelve cases of from 3.6 to 3.84 mg.).

10. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.

11. Okey, R.; Stewart, M. J., and Greenwood, M. L.: Studies of the Metabolism of Women, J. Biol Chem. **87**:91, 1930.

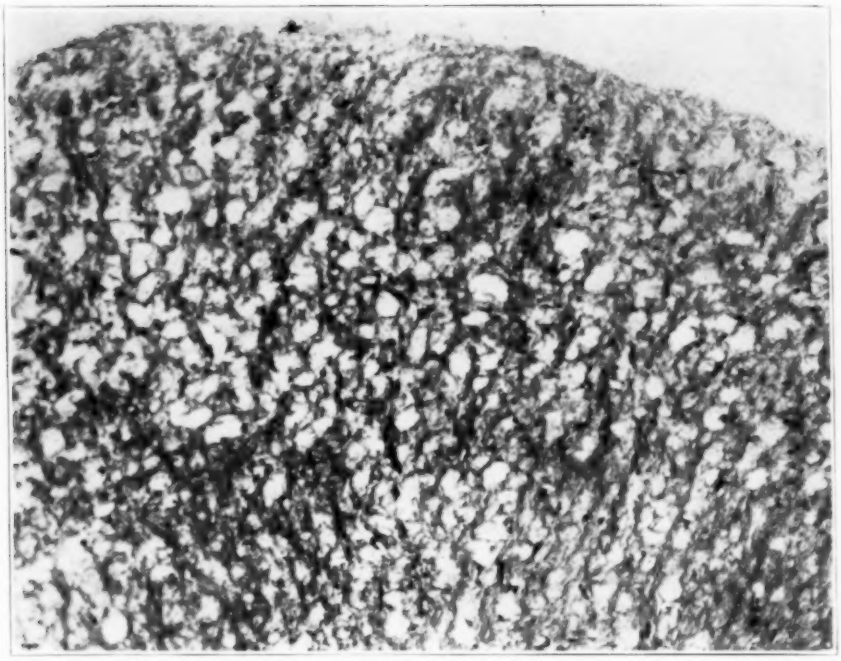

Fig. 1 (experiment I-9).—Case of multiple sclerosis no. 11. This photomicrograph and the following ones are from transverse sections through rats' spinal cords, stained with Weil's method for myelin sheaths, which had been incubated for twenty-four hours at 37 C. with the serum or lipase solutions. This demonstrates the appearance of a section that had been graded ++. Leitz objective × 10; ocular, × 6.

Fig. 2 (experiment XIV-5).—Case of multiple sclerosis, no. 28. The demyelinating effect of the serum on this spinal cord had been graded ++. Zeiss objective 3 mm.; ocular × 10.

The blood in our cases was immediately centrifugated after it had been received in the laboratory, with an interval between venous puncture and centrifugation varying from a few minutes to a maximum of three hours. The serum was directly precipitated with trichloracetic acid or, as in the earlier cases, preserved in the icebox over night. With a few exceptions the blood was taken shortly before the lunch hour.

In order to find out whether or not different modes of living and diets and the duration of the disease might produce different levels of inorganic phosphorus in the blood, the cases were divided into five groups, as shown in table 5.

TABLE 5.—*Distribution of Patients Among Hospitals*

	Number of Cases	Number of Examinations
I. Northwestern University Dispensary	8	16
II. Cook County Hospital	8	14
III. Oak Forest Infirmary	19	32
IV. Montefiore Hospital, New York	6	12
V. State Hospital, Madison, Wis. (Dr. Crandall)	5	5
Total	46	79

TABLE 6.—*Inorganic Phosphorus in the Serum of Patients with Muliple Sclerosis* *

	Phosphorus, Mg. per 100 Cc. Serum		
	Maximum	Minimum	Average
I. 3.1, 3.2, 3.3, 3.3, 3.5, 3.9, 4.0, 4.3	4.3	3.1	3.5
II. 3.0, 3.2, 3.2, 3.2, 3.2, 3.4, 3.6, 4.1	4.1	3.0	3.4
III. 2.6, 2.6, 2.9, 3.0, 3.0, 3.0, 3.1, 3.1, 3.1, 3.2, 3.2, 3.4, 3.4, 3.5, 3.5, 3.9, 3.9, 4.0, 4.0	4.0	2.6	3.2
IV. 3.3, 3.6, 3.8, 3.8, 4.5, 4.6	4.6	3.3	3.9
V. 3.0, 3.1, 3.4, 3.6, 4.0	4.0	3.0	3.4
Total	4.6	2.6	3.4

* Roman numerals correspond to the hospitals in table 5.

The results of the tests are shown in table 6.

Furthermore, for comparison, serums were investigated from hospital patients who lived under conditions similar to those of the patients with multiple sclerosis and who were handicapped by lesions of the spinal cord (four cases) or hemiplegia (six cases) or suffered from other chronic diseases (twenty-four cases). The age of these patients and of the normal controls did not exceed 50.

One case of multiple sclerosis was not included in the tabulation because the patient showed an extremely high phosphorus value (7 mg. and, five weeks later, 5 mg.) and was suffering from nephritis and the after-effects of infected bedsores. The two high values of 4.5 and 4.6 mg. in the Montefiore Hospital group were for two women who were bed-ridden. Two cases occurring in hospital patients were omitted: One was a case of polycythemia with 24.8 mg. of inorganic

phosphorus; the other was a case of pernicious anemia with subacute combined degeneration and 2.2 mg. of inorganic phosphorus.

The values shown in table 7 are averages of the results of different examinations of the same patients, made at intervals of approximately four weeks, several times in sixteen of the patients with multiple sclerosis and once or twice in the others.

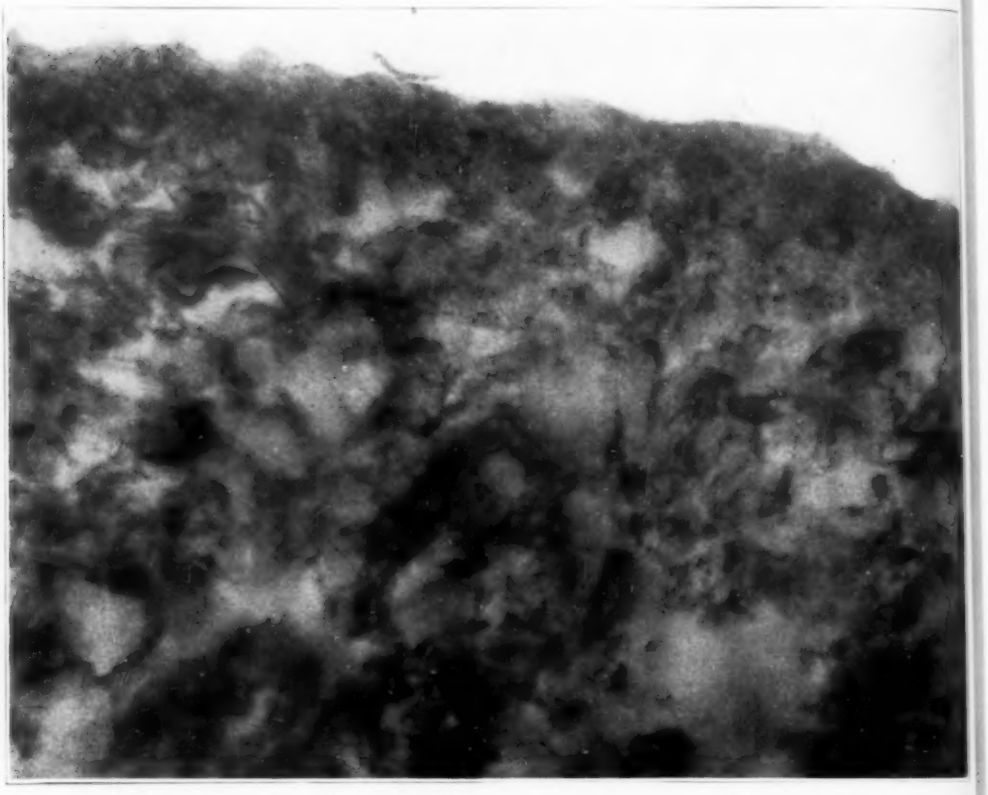

Fig. 3 (experiment X).—Case of multiple sclerosis, no. 4. This demonstrates the effect of serum on rat spinal cord graded +++. Zeiss objective 3 mm.; ocular × 10.

In a number of cases the amount of protein in the serum was determined by calculating the total nitrogen content of the serum by the Kjeldahl method.

The cases of multiple sclerosis did not show any appreciable difference from normal values and those found in the other diseases, listed in the footnote to table 7.

TABLE 7.—*Inorganic Phosphorus in the Serums of Different Groups of Patients*

Inorganic Phosphorus, Mg. per 100 Cc. of Serum	Patients with Multiple Sclerosis		Normal Patients		Hospital Patients*		Syphilitic Patients	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
2.5-2.6	2	4	..	..	..	..	..	..
2.7-2.8	..	..	..	..	..	..	..	..
2.9-3.0	6	13	..	..	..	..	..	..
3.1-3.2	11	24	..	..	1	5	..	..
3.3-3.4	8	18	..	..	1	5	1	8
3.5-3.6	6	13	2	13	3	14	..	..
3.7-3.8	2	4	2	13	3	14	2	15
3.9-4.0	7	15	5	33	3	14	1	8
4.1-4.2	1	2	3	20	5	24	2	15
4.3-4.4	1	2	2	13	3	14	..	..
4.5-4.6	2	4	..	..	..	..	4	31
4.7-4.8	..	..	1	7	2	9	2	15
4.9-5.6	..	..	..	..	..	..	1	8
Mean value, Mg. of phosphorus in 100 cc. of serum	3.4		4.0		4.2		4.4	

* The 21 different hospital cases, with the phosphorus content in each, were: 4 spinal cord lesions (3.7, 3.9, 4.1 and 4.1); 1 skull fracture (4.8); 2 alcoholic neuritis (3.6 and 4.4); 6 hemiplegias (arteriosclerotic) (3.2, 3.3, 3.5, 3.7, 4.0 and 4.3); 2 hyperthyroidism (4.0 and 4.2); 1 manic-depressive psychosis (4.1); 1 hypertension (4.2), and 4 not diagnosed (3.5, 3.8, 4.3 and 4.7).

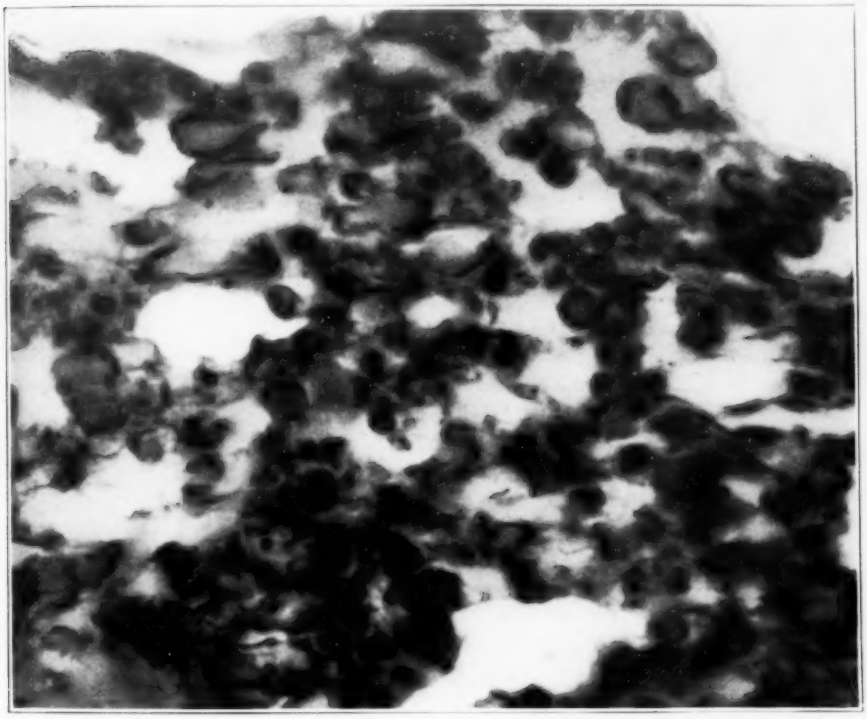

Fig. 4 (experiment XVIII-4).—Pancreas lipase effect on rats' spinal cord. Dilution of pancreas-glycerin extract 1:80 with phosphate buffer solution of p_H 7.6. Olive oil splitting effect of lipase = 9 + (1.8 cc. of twentieth-normal sodium hydroxide). This demonstrates the absence of any demyelinating effect. Zeiss objective 3 mm.; ocular × 10.

TABLE 8.—*Nitrogen and Phosphorus Content of the Serums of Different Groups of Patients*

Patients with Multiple Sclerosis		Hospital Patients			Syphilitic Patients	
Mg. Nitrogen in 100 Cc. Serum	Mg. Inorganic Phosphorus in 100 Cc. Serum	Number	Mg. Nitrogen in 100 Cc. Serum	Mg. Inorganic Phosphorus in 100 Cc. Serum	Mg. Nitrogen in 100 Cc. Serum	Mg. Inorganic Phosphorus in 100 Cc. Serum
1050	2.9	4	1020	3.3	1050	4.7
1080	2.9	4	1060	3.7	1090	3.6
1110	5.0	4	1130	4.0	1110	3.3
1120	2.6	1	1230	4.0	1130	4.6
1370	3.6				1270	3.8

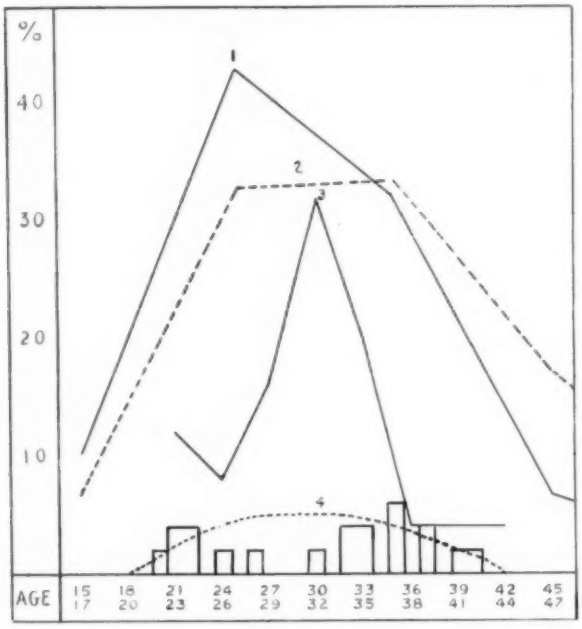

Fig. 5.—Chart illustrating distribution of age at the onset of the disease. Curve *1* gives the figures in Allison's 59 cases of multiple sclerosis; curve *2*, in 692 different cases of multiple sclerosis collected by Allison from the literature; curve *3*, in 26 of our own cases of multiple sclerosis; curve *4*, in cases of osteomalacia (from S. Hirsch [München. med. Wchnschr. **67**:1087, 1920]), and in 22 cases of Schilder's disease from Gasul (number of cases indicated by columns at bottom of chart). The abscissa represents ages in years; the ordinate the per cent of the total cases.

Fourteen spinal fluids were examined and compared with twelve spinal fluids from patients not suffering from multiple sclerosis. The Lange colloidal gold test was done, together with the Nonne test for globulin and the determination of the total phosphorus. The results are shown in table 9.

Eleven of fourteen spinal fluids (79 per cent) from cases of multiple sclerosis showed a positive colloidal gold reaction: Seven (50 per cent) gave a reaction of the type of dementia paralytica; three (22 per cent), of the syphilitic type, and one was as high as 2, lilac.

The method applied was Novick's modification of Lange's colloidal gold test. The gold solution was standardized in such a way that 5 cc. gave, with 1.7 cc. of a 1 per cent solution of sodium chloride, an immediate change to violet, without, however, being completely decolorized within one hour. We used this modification because the standardization, as recommended by Novick and applied by Chevassut, has proved to be too sensitive.

TABLE 9.—*Results of Laboratory Examination of Spinal Fluids of Patients with Multiple Sclerosis*

Case	1	4	8	9	11	12	15	16	17	21	23	24	25	28
Colloidal gold test	—	+	+	—	+	—	+	+	+	+	+	+	+	+
Nonne test	1	+	—	—	+	—	—	—	—	—	—	—	++	—
Total phosphorus	2.1	2.4	1.8	1.9	2.1	2.0	2.1	1.5	2.1	2.3	2.7	1.6	2.5	2.2
Inorganic phosphorus in serum	3.2	2.9	3.3	3.2	2.6	2.7	3.2	2.9	2.9	7.0	3.3	3.2	3.4	3.3

Twelve spinal fluids from other diseases: 1.6, 1.7 (2 cases), 1.8, 2.1, 2.2 (2 cases), 2.3 and 2.4 (4 cases) mg. of phosphorus per hundred cubic centimeters of fluid. Average for fourteen spinal fluids from cases of multiple sclerosis: 2.1 mg. of phosphorus. Average for twelve other spinal fluids: 2.2 mg. of phosphorus.

COMMENT

For nearly fifty years, research in multiple sclerosis has been under the influence of the theory of Pierre Marie (1884) of the infectious origin of the condition. Attempts to transfer the disease from animal to animal or to demonstrate an infectious organism have never been convincingly carried through (O. Teague). The claim of Steiner that, though it is not possible to demonstrate spirochetes in every case of multiple sclerosis, the argentophil granules, rings and disks found are the débris of spirochetes has been criticized by Lüthy.[12] Based on the work of Bullock (1913), the possibility of a filtrable virus has frequently been considered, and the climax of this idea has been the claim of Chevassut and Purves-Stewart; this cannot be sustained by our own investigations and has also been rejected by Carmichael.[13] Deductions made from an apparent histologic similarity with cases of acute disseminated encephalomyelitis following measles, smallpox and vaccination have been made another basis of the assumption of a filtrable virus as the etiologic agent in multiple sclerosis. Walthard[14] has shown that such similarity cannot be demonstrated if one goes into a more

12. Lüthy, F.: Zur Frage der Spirochätenbefunde bei multipler Sklerose Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:290, 1930

13. Carmichael, E. A.: The Aetiology of Disseminated Sclerosis, Proc. Roy Soc. Med. **24**:591, 1931.

14. Walthard, K. M.: Deutsche Ztschr. f. Nervenh. **111**:1, 1929.

detailed histopathologic analysis. Greenfield [15] has summarized all the more recent hypotheses by stating that, without experimental evidence, "we are likely to remain in complete ignorance of the nature of the viruses which cause them, and any hypothesis as to their relationship to one another must be accepted with caution."

Marburg has never entirely given up his theory (1909) that a ferment acts destructively on the myelin sheaths. Brickner's [3] observations that plasmas from multiple sclerosis act more destructively on rats' spinal cords than do normal plasmas can be supported by our own investigations on serums. It should be emphasized, however, that a like amount of destruction may be seen in other diseases, and that the number of cases of multiple sclerosis that show only a mild reaction and of normal cases that show an intensive reaction is rather large. It seems premature to assume a direct relationship between the increase in lipase in the serum of patients suffering from multiple sclerosis and the demyelinating action of such serums on rats' spinal cords. It has to be shown why such action is absent under other pathologic conditions associated with an increase of lipase. Furthermore, our experiments with very active pancreas lipase and rats' spinal cords did not support the theory that the changes produced by serums and plasmas from cases of multiple sclerosis are caused of necessity by a lipolytic ferment.

Struempell [16] and with him Mueller still assume an endogenic origin of the disease, in the form of a primary disease of the glia. Hassin [17] considered this endogenic factor to be an unknown toxin, and concluded from histologic studies that multiple sclerosis is a primary demyelinization and not an infectious disease. From our own experiments such possibilities of demyelinization by an endotoxin have been demonstrated with different substances, among others sodium taurocholate (Weil [18]). Putnam [19] demonstrated plaques in the brains and spinal cords of dogs following the injection of tetanus toxin.

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15. Greenfield, J. G., in Browning, C. H.; Bulloch, W.; Dible, J. H., and others: A System of Bacteriology, London, His Majesty's Stationery Office, 1930, vol. 7, p. 138.

16. Struempell, A.: Zur Pathologie der multiplen Sklerose, Neurol. Zentralbl. **15**:961, 1896.

17. Hassin, G. B.: Pathology of Multiple Sclerosis, New York Association for Research in Nervous and Mental Diseases, 1921, vol. 2, p. 144.

18. Weil, A.: The Effect of Hemolytic Toxins on Nervous Tissue, Arch. Path. **9**:828 (April) 1930; Die Wirkung von Schlangengiften auf Nervengewebe, Arch. f. exper. Path. u. Pharmakol. **154**:228, 1930.

19. Putnam, T.: Acute Multiple Sclerosis in Dogs, Arch. Neurol. & Psychiat. **24**:640 (Sept.) 1930.

During the last decade more material has accumulated that has shown that primary demyelinization of peripheral nerves and of the central nervous system may be brought about in animal experiments by diets deficient in some vitamins. As examples may be cited the work of Gildea, Kattwinkel and Castle in dogs,[20] of De Aberle, Zimmerman and Brill [21] in rats following vitamin A deficiency and of Hughes, Lienhardt and Aubel [22] in pigs, chickens and cows. In the last mentioned experiments the lack of vitamin A produced impaired vision, incoordination and spasms clinically. Histologically, demyelinization was seen in portions of the spinal cord and in the optic, sciatic and femoral nerves in Marchi preparations.

Our own observation of a content of inorganic phosphorus of less than 3.3 mg. in 40 per cent of the cases was contrary to the expectation of a high amount in a disease that is associated with a rapid breaking down of nerve substances. In syphilitic cases, especially in cases of dementia paralytica, there was an increase in the inorganic phosphorus as expected. We are well aware that the number of cases examined is much too small to permit drawing definite conclusions. It was thought, however, that they might stimulate other research along this line. It seems that the duration of the disease and dietary factors play a rôle in the low phosphorus level.

There exists the possibility that the increase in lipase and decrease in phosphorus are only secondary manifestations of a primary lesion of other organs of the body, e.g., the liver, and that such a lesion eliminates a myelolytic toxin or prepares the way for the passing of toxic metabolic products through the hemato-encephalic barrier. Lesions of this kind may be brought about in infectious diseases. They occur in acute disturbances of the metabolic equilibrium, as in pregnancy or following operations with narcosis of long duration or severe trauma to the nervous system, all of which are conditions that are known to favor the beginning of multiple sclerosis. On the other hand, disturbances of lipase and phosphorus metabolism may also be sequelae to a primary disease of the central nervous system with interference with the normal nervous mechanism of the supervision of this metabolism.

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20. Gildea, E.; Kattwinkel, E. K., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

21. DeAberle, S. B.; Zimmerman, H. M., and Brill, L.: Paralysis in Rats on a Vitamin-A-Low Diet, Anat. Rec. (supp.) **48**:7, 1931.

22. Hughes, J. S.; Lienhardt, H. F., and Aubel, C. E.: Nerve Degeneration Resulting from Avitaminosis A, J. Nutrition **2**:183, 1929.

SUMMARY AND CONCLUSIONS

1. In twenty-six cases of multiple sclerosis the influence of the patient's serum on the spinal cord of the rat was studied. In agreement with Brickner's experiments with plasma of patients with multiple sclerosis it was found that a larger number of serums from cases of multiple sclerosis than of normal serums acted destructively on the spinal cords of rats. Such action, however, could also be demonstrated in serums from other diseases, and the difference did not seem to be large enough to warrant the drawing of conclusions as to the importance of increase in lipase in the etiology of multiple sclerosis. Furthermore, experiments with active pancreas lipase on the spinal cords of rats gave a negative result.

2. The amount of inorganic phosphorus in the serum of patients with multiple sclerosis was 3.4 mg. per hundred cubic centimeters on the average as compared with 4 mg. in normal cases, 4.2 mg. in twenty-one cases of eight different diseases and 4.4 mg. in cases of syphilis of the central nervous system. In 40 per cent of the cases of multiple sclerosis the inorganic phosphorus of the serum was below 3.3 mg., and in 65 per cent it was 3.5 mg. or less.

ATYPICAL DIFFUSE SCLEROSIS *

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The literature of the last fifty years contains a relatively small series of observations of what is called diffuse sclerosis. This disease is histopathologically not an entity, and its clinical picture is still difficult to interpret. From a pathologic point of view, it can be divided into three subdivisions: (1) purely degenerative in character; (2) with inflammatory phenomena, and (3) with diffuse gliomas. The last type, strictly speaking, does not belong to diffuse sclerosis. The degenerative and inflammatory groups can be finally subdivided into typical and atypical cases. The changes in typical cases consist chiefly of a widespread destruction of the white matter of both hemispheres and, frequently, also of that of the cerebellum. The deeper layers of the white matter are more severely affected than the superficial ones, the fibrae arcuatae remaining fairly well preserved. The axis cylinders persist longer than the myelin sheaths. In the area of destroyed white matter, manifold glial reactions are, as a rule, observed. They are not specific for diffuse sclerosis, and appear wherever large masses of myelin undergo a more or less complete destruction. Connective tissue proliferation originating from blood vessel sheaths is likewise of frequent occurrence. The gray matter, on the contrary, is affected only in restricted areas, and the same can be said of the meninges. The only difference between the so-called degenerative and inflammatory cases consists in the presence of infiltrative processes in the latter, consisting of lymphocytes, plasma cells and sometimes polyblasts.

Atypical observations, both clinical and pathologic, have been reported so far in a few instances only. Their divergence from the typical picture lies in the extensive involvement of the gray matter (A. Jakob [2]) or in the presence of peculiar metabolic products in the white matter (Kaltenbach [3]).

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* From the State Psychopathic Hospital, Ann Arbor, Mich., and the Boston Psychopathic Hospital, Boston.

1. Footnote deleted by author.

2. Jakob, A.: Anatomie und Histologie des Grosshirns, Vienna, Franz Deuticke, 1929, vol. 2, p. 849.

3. Kaltenbach, quoted by Jakob (footnote 2, p. 855).

The clinical picture is, as we have already said, frequently difficult to interpret. The disease may appear at any age, showing a certain predisposition for infancy, but many cases appear in the third or fourth decade, and even the senium is not free from it (Guttmann [4]). The psychic symptoms are not characteristic; the children may be restless and irritable or, on the other hand, unusually quiet, or in some cases excited; epileptic seizures, hemiplegia and tetraplegia are frequent; focal symptoms suggesting a brain tumor, multiple sclerosis or even arteriosclerotic changes (in adults) have been reported. Muscle atrophies (such as of the tongue or extremities) are rare. Choked disks, blindness and deafness are common observations. The duration of the disease varies from several weeks to two years; in a few instances, however, it reaches from ten to fifteen years.

The uncertainty of the clinical diagnosis, on the one hand, and the monotony of the histopathologic picture, on the other, led B. Sachs [5] to state that at the present time more clinical data ought to be collected. We wish to add that atypical histopathologic observations are of no less interest than the completion of the clinical picture, and as our observations contain both new clinical and new pathologic points, we are presenting a case.

REPORT OF A CASE

Clinical History.—E. F., a white man, aged 26, single, a musician, admitted to the Taunton State Hospital, in January, 1919, had been noted in October, 1918, to talk incoherently and to entertain delusions that his father was a Russian spy and that he himself had a secret that would make him rich. Neurologically, the positive changes were: In walking, he dragged the right foot; coordination tests were within normal limits; the deep tendon reflexes of the right upper and lower extremities were greater than those of the left; sensation of touch was diminished on the right side. The only cranial nerve disturbance was that of slightly irregular pupils. At this time a diagnosis of dementia praecox was ventured.

In the months of December, 1919, and March and October, 1920, he had a generalized convulsion with slight mental confusion afterward. In 1922, neurologic examination at Westboro State Hospital, to which he had been transferred, showed an increased disturbance in gait in that he could walk only with support, both feet describing semicircular arcs, less pronounced on the left side. The deep tendon reflexes in the right lower extremity were increased so that an ankle clonus was present; on the left they were increased, but there was no ankle clonus. Atrophy of the intrinsic muscles of the right hand and to a lesser degree of the left hand and also in the right shoulder girdle was observed. Because of the progressiveness of the disease, a tentative diagnosis of progressive muscular atrophy was now made.

The disease became progressively worse, so that in 1926 the patient was unable to walk; he could not flex the legs. Deep and superficial sensation was lost in both lower extremities, and he became incontinent of both urine and feces. Occa-

4. Guttmann, E.: Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:1, 1925.

5. Sachs, B., in discussion of Shelden, W. D.; Doyle, J. B., and Kernohan, J. W.: Encephalitis Periaxialis Diffusa, Arch. Neurol. & Psychiat. **21**:1270 (June) 1929.

sional convulsive seizures occurred irregularly, and memory gradually became poorer. He complained of dizziness and headaches. The convulsions increased in number and on Nov. 9, 1929, he died of bronchopneumonia.

Laboratory studies showed a negative Wassermann reaction of the blood. In 1922, the spinal fluid showed ++++ globulin and albumin. The colloidal gold curve was 1111233211. In 1924, tests showed albumin and globulin +++, colloidal gold 0002421000 and 15 cells per cubic millimeter.

Summary.—A man, aged 26, in 1919, at times talked incoherently and expressed delusions of a paranoid nature. Neurologically, a progressive disturbance in gait occurred with bilateral hyperreflexia, more marked on the right, which eventually caused him to become bedridden. Atrophy of the intrinsic muscles of both hands occurred. Sensation in the lower extremities was diminished. Convulsions occurred with increasing frequency, leaving memory impaired. He died eleven years after the onset of the illness.

Gross Description of the Brain and Spinal Cord.—The meninges showed no gross changes. The convolutions were of normal appearance and the basal vessels smooth. The brain, which was preserved in formaldehyde, was of firm consistency.

Left Hemisphere: Frontal sections showed: The gray matter was of normal width and clearly outlined, but the white matter of the frontal lobe showed a peculiar yellowish-gray tinge which soon became more reddish. The consistency of the white matter was unusually firm. The blood vessels could be seen as deep red points, and appeared to be calcified. The central part of the white matter was most strikingly changed, whereas the peripheral parts were softer and more yellow. In the anterior part of the parietal lobe the white matter was almost unchanged, and contained only a few scattered yellow foci. The process appeared again toward the posterior part, involving practically all the white matter of that lobe. The color was the same as that of the frontal lobe. The gray matter appeared pale and indistinct. In the calcarine region the white matter showed a slight yellow change, and the gray matter could be seen clearly. The white matter of the temporal lobe was slightly yellow, but the gray matter was well outlined (fig. 1).

The caudate nucleus was not clearly outlined, and appeared somewhat darker than normal. It contained a milky focus as large as a green pea. The putamen was misshapen and hard in consistency, as were the pallidum and the internal capsule. The latter was narrow and indistinct. The anterior commissure, perforated substance and thalamus were distinctly outlined. The cornu ammonis appeared to be normal. The left ventricle was narrow.

Right Hemisphere: In the frontal lobe the white matter was transformed into a yellow tissue like that of the left hemisphere, and contained numerous pinhead-sized foci of the same appearance as those in the left. In the white matter of the remaining lobes there were several scattered yellow foci as large as a 50 cent piece. The basal ganglia and the gray matter appeared to be normal. The right ventricle was narrow like the left. The substantia nigra was distinctly visible. No gross changes were found in the pons.

Cerebellum: The white matter of the left hemisphere was transformed throughout, in the same way as the white matter of the left hemisphere of the brain (fig. 1), whereas sections through the right hemisphere showed only several yellow foci as large as 10 cent pieces. The choroid plexus appeared to be normal.

Spinal Cord: No foci similar to those seen in the brain were found.

The long duration of the disease in our case tends to give different pictures of myelin destruction from those described by most authors. In the affected areas

most of the myelin has long since disappeared, and we are dealing chiefly with glial and connective tissue repair processes, which are continuously going on and are of pathologic importance.

Microscopic Appearance.—Nissl Stain: The process was most severe in the parietal and frontal lobes, and less so in the temporal and occipital lobes. In the latter a considerable amount of well preserved myelin was still recognizable.

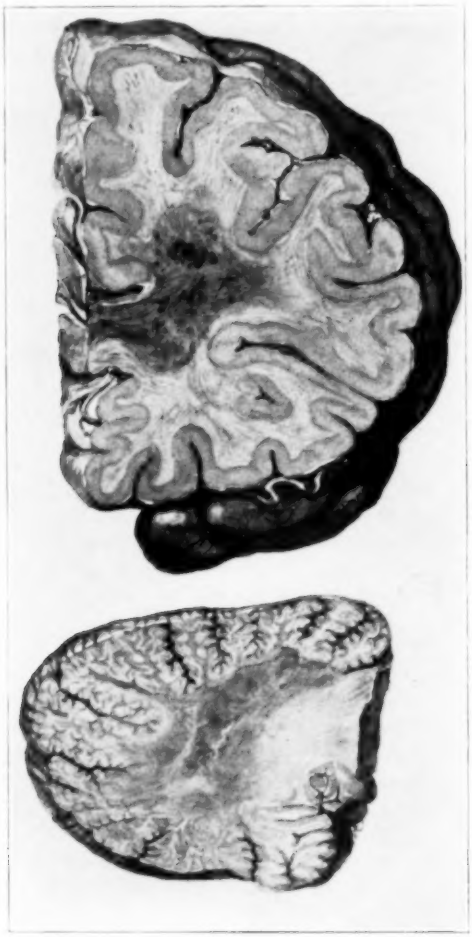

Fig. 1.—Section through brain and cerebellum showing the destruction of the white matter.

In the superficial portion of the white matter, the axis cylinders and occasionally the myelin in the convolutional crests were relatively well preserved, even in the most affected regions, while in the deep portions of the white matter the myelin and axis cylinders were entirely destroyed (fig. 2). In the regions where the myelin was absent, the white matter had been broken down and completely dissolved, whereas in the areas where myelin was still present (fig. 2, upper part) it had undergone so slow a degeneration as hardly to be visible even microscopically.

The left cerebral and cerebellar hemispheres were more involved than the right. The cerebellum was the most heavily involved, and in the left hemisphere Spielmeyer's stain showed only a few isolated myelin sheaths. In the regions of the cerebellum, where the myelin was still preserved, Nissl's stain revealed a slight glial irritation and a proliferation of capillaries, which were still more striking in tannin-silver preparations. Here the leptomeninges and the gray matter showed nothing of importance.

A markedly contrasting picture was observed in those regions of both forebrain and cerebellum where the myelin had been completely destroyed; grossly they had a reddish-yellow tinge. The chief histologic changes occurred in the blood vessels, which could be seen with the naked eye. They appeared as glassy trans-

Fig. 2.—Widespread destruction of myelin in the deep layers of the white matter. The myelin of one convolution is well preserved. The U-fibers are recognizable. Large masses of hyalin are seen in the deep layers of the white matter. Spielmeyer's stain; × 10.

parent lines or disks, depending on the direction in which the section was cut, and could be easily distinguished from the general milky appearance of the unstained celloidin or frozen sections.

In the block they had mostly the appearance of discrete lesions, the size of a pinhead or a little larger (fig. 1). A particularly distinct focus of translucent appearance, the size of a pea, was found in the left caudate nucleus. The lesions described were found scattered through the white matter of both hemispheres, except in the occipital and frontal lobes. In the left hemisphere of the cerebellum practically all the myelin had been replaced by this peculiar pathologic product

(fig. 1). Similar but not so pronounced was the destruction in the right hemisphere of the cerebellum.

Histologic examination of the transparent areas showed definitely that this peculiar change represents the last stage of this disease. For the sake of clarity one must consider the pathologic changes in chronologic order. The process in the cerebrum is identical with that in the cerebellum, and one description in general suffices for both. When differences occur they will be so designated. The spinal cord will be described separately.

Evolution of the Condition: The apparent earliest change seen is a marked proliferation and swelling of the capillaries and the small vessels. The walls of these are thickened, and are rich in cells, with round or oval nuclei and abundant cytoplasm. Sometimes several layers of cells are seen; still the intima is not much swollen, so that the lumen, though narrowed, remains patent. Tannin-silver preparations show a slight but definite proliferation of the adventitia, which is often infiltrated with plasma cells and lymphocytes, varying from a few cells to dense masses. Sometimes the oligodendroglia is considerably increased, and gives the impression of an infiltration. These visible changes of the blood vessels, found in almost all parts of the central nervous system, are most marked in the cerebellum, and are absent in the pons, medulla and spinal cord.

The severity of the process and its true nature cannot be observed from a Nissl section, but can be better studied in Mallory's aniline blue-orange "g" method. The latter shows that the process has continued long after the destruction of myelin, and reveals further that there are severe and important changes in the gray matter and the meninges, in that the barrier between nerve tissue, leptomeninges and blood vessels has undergone a fundamental change.

A marked change takes place in the white matter, parenchyma and membrana limitans of the affected areas, so that the normal structure disappears and the ground tissue consists of a fine network of fibers, large forms of microglia and a few vessels (fig. 3). In these involved areas are large masses of pathologic products that stain yellow, orange and bright red. Without doubt these are myelin remnants, because they are most numerous in the white matter and are found in the same location as the myelin fragments in the Weigert sections. These products are seen as small droplets which become converted into large, shapeless masses, finally reaching the meninges through the membrana limitans (fig. 4). This strange migration from the white matter through the parenchyma into the meninges is made possible because of marked damage to the membrana limitans, which has become a spongy network containing no glia cells and only a few glia fibers and blood vessels (compare figs. 3 and 4).

The change previously described suggests that the process is beyond the control of the usual physiologic mechanism, and the tissue is converted into a network of fibers in which are suspended débris in tissue fluid which spreads in all directions. These changes occur especially in the cerebellum and small isolated foci in both cerebral hemispheres.

Another picture occurs in different parts of the cerebrum and cerebellum in glial scar formation, with subsequent connective tissue proliferation and final hyaline degeneration.

In Nissl pictures, the glial scar consists of a dense tissue containing oval nuclei in long rows which occasionally interlace. This tissue is particularly dense around blood vessels. The vessels are often thickened by proliferation of the different elements of their walls, and they are surrounded by large masses of plasma cells

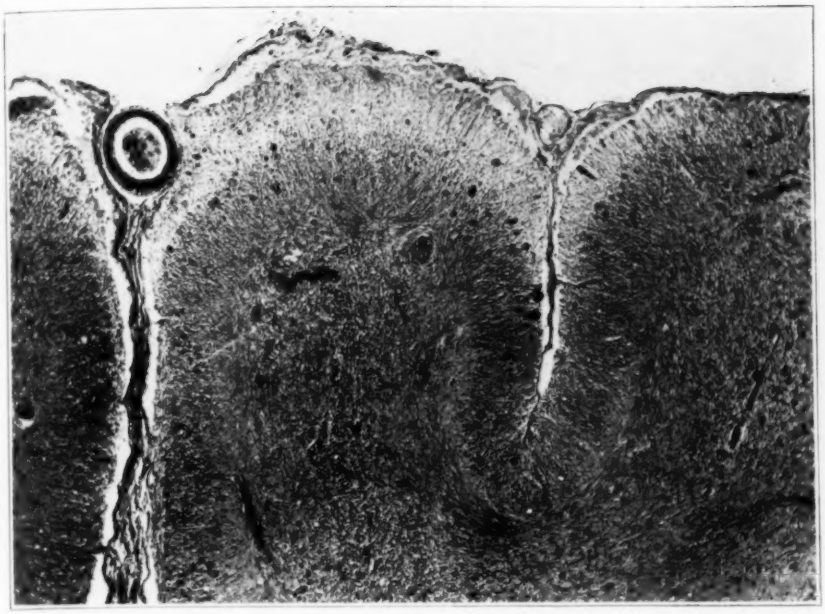

Fig. 3.—Most severe rarefaction of the membrana limitans and the molecular layer which contains numerous metastatic products. The granular layer and white matter are destroyed. Left cerebellar hemisphere. Mallory aniline blue stain; × 50.

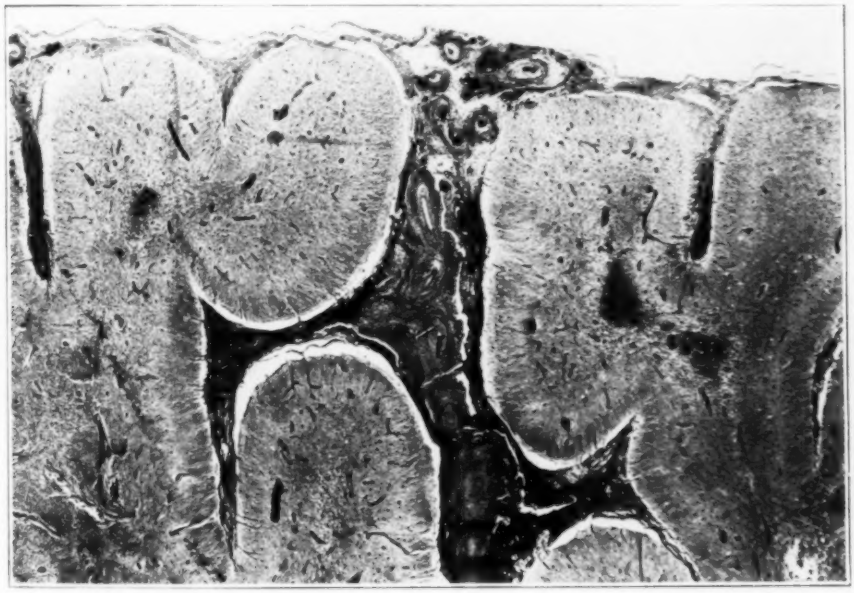

Fig. 4.—Metabolic products in the white matter of the left cerebellar hemisphere. Destruction of myelin and granular layer. Severe hyalinization of the pia vessels. Mallory stain; × 50.

and lymphocytes (fig. 5). The glial scar formation stains pink in aniline blue sections and has a very closely woven structure, and the form of the cells is not recognizable as in Nissl preparations. The form of the elements is best seen by the Bielschowsky method. It shows large, slightly oval or spindle-shaped cells with large nuclei situated at the periphery of the protoplasm, with a thick fiber at each pole of the cell. These resemble astrocytes more than any other type of cell, but are not identical and stain very weakly with gold sublimate. The glial scar consists almost wholly of these elements and a dense fiber network, the myelin being completely dissolved. A few axons are seen here and there. The scar tissue shows very little evidence of acute reaction. Occasional small foci of hypertrophic glia cells can be found, especially in the basal ganglia; there are also accumulations of microglia cells, but these are few in number.

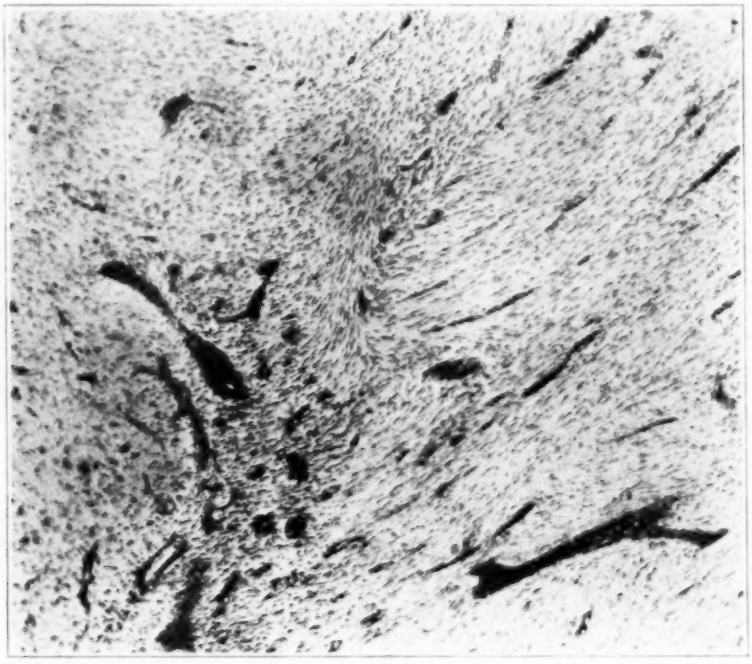

Fig. 5.—Interlocking glial scar of the white matter. Blood vessel proliferation and infiltration. Left brain hemisphere. Nissl stain; × 50.

This type of glial tissue appears to replace the destroyed myelin throughout the cerebrum, and repair thus takes place. But the formation of the glial scar in no sense means a definite end to the disease, as very soon there can be observed an unusual tissue activity in the scarified areas. Large masses of fibroblasts, plasma cells and lymphocytes penetrate the glial tissue. The blood vessels are swollen and surrounded by dense infiltrations. In this way the almost inactive scar is involved in an exceedingly actively proliferating process. Nissl preparations now reveal very cellular, deep blue stained areas in which the structures of the glial scar disappear entirely. An intensive fiber production sets in at the same time, and accordingly van Gieson sections show numerous deep red connective tissue fibers.

Tannin-silver sections, however, give the most definite information as to the extent of the connective tissue proliferation, and show the gradual increase of the reaction. First it is restricted to the vessel walls proper, and then a few and later more fibers penetrate the glial scar in all directions (fig. 6).

At this stage, Mallory's aniline blue stain shows many interesting features: The connective tissue is unusually dense and stains intensely blue. It contrasts sharply with the pink-staining glial scar which it overruns and gradually supplants. A combined connective and glial scar tissue results, in which the connective tissue becomes more and more prevalent (fig. 6). When this stage is reached the proliferative reparation is definitely completed, and the degenerative phase begins.

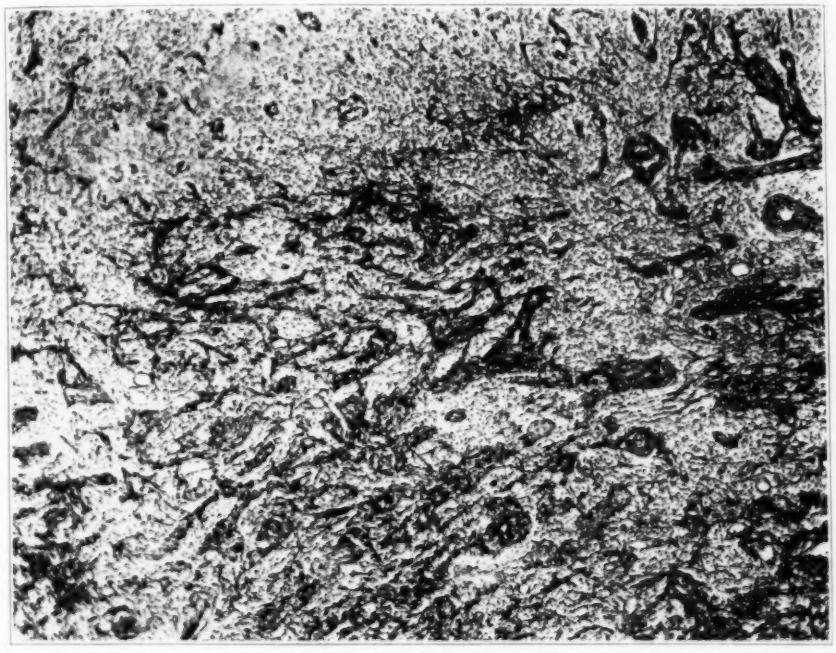

Fig. 6.—Most pronounced connective tissue proliferation originating from the adventitia; white matter of the left brain hemisphere. Achucarro-Clarfeld stain; × 50.

As in the preceding stage, it is the blood vessels, chiefly the small arteries, that are affected. The fibrils of the media swell, lose their slender form and become broader, staining a weak grayish blue with thionine. The nuclei swell at first, later shrink and finally disappear. The swelling of the myofibrils advances, they become structureless and shapeless, and are transformed into hyaline or gelatinous masses that occupy the entire media. The degeneration spreads from the media to the adventitia, whereas the intima remains intact for some time (fig. 7). The vessel wall in this stage is much thickened and contains but few recognizable structures. Finally they all disappear, the lumen becomes filled with hyaline masses which finally close it, and the vessel is transformed into a structureless, shapeless, transparent tissue (figs. 7 and 8).

This process is not confined to the vessel walls, but spreads among the surrounding connective tissues in a like manner. The connective tissue fibers swell and lose their structure (are reduced to hyalin); the hyaline masses fuse, and the large transparent foci mentioned earlier are formed and visible in unstained sections (figs. 7 and 8).

The change is restricted to the structures of mesodermal origin. One can observe the transformation of fibroblasts in the same way as that of the fibers; they become finally a homogeneous drop. The tissue is completely destroyed, and no trace of connective tissue fibers can be found. Such a process is not observed in the glia cells.

This is the last stage of the tissue disintegration in which the nerve tissue as well as the connective tissue scar undergoes a complete destruction. The disease has come to a definite end.

The pons, medulla and spinal cord are free from such changes.

The gray matter of the brain is not quite free from changes. These do not affect the parenchyma primarily, but are confined to the cortical blood vessels; the change is a very limited one and is identical in character with that in the white matter. Most of the affected vessels are completely hyalinized, the ganglion cells nearby are changed in a nonspecific way, and there is a marked proliferation of glia. Cajal's gold chloride method shows a large number of hypertrophied astrocytes. Connective tissue proliferation is much less marked than in the white matter. Here and there small foci of adventitial proliferation occur.

The destruction of parenchyma is much more pronounced in the cerebellum. The granular layer shows an extensive rarefaction. Morphologically, its blood vessel changes are identical with those already described, i. e., a swelling of the myofibrils, subsequent destruction of the walls and spread of the degeneration into the meshes of the pia-arachnoid, with transformation finally into hyalin. The degenerated vessels of the meninges are surrounded by tissue fluid which penetrates the broken-down first layer and membrana limitans, and becomes mixed with lymphocytes, plasma cells and pathologic products of different origin. These factors produce histologic pictures of unusual variety (fig. 8).

In only a few instances a final calcification of the hyalinized blood vessels could be seen, as, for example, in the dentate nucleus and in several limited foci in the white matter of the left parietal lobe. This process, however, is an exception.

Basal Ganglia: On the left side the whole caudate nucleus is misshapen and contains glial scar foci. One such lesion, the size of a small cherry, projects into the ventricle and compresses the internal capsule on one side, while a smaller focus in the pallidum compresses it from the other side, thereby decreasing the width of the internal capsule to one third of its normal size. The glia in some places is very active, and multinucleated astrocytes are seen. The thalamus shows less involvement.

On the right side the caudate nucleus contains the transparent focus, the size of a pea, mentioned earlier in the gross description, and numerous small scar foci. The putamen, pallidum and internal capsule are free. The corpus callosum shows extensive glial scar formation with proliferation of the blood vessel walls and extensive infiltration of the adventitia.

Nothing definite can be said of the microchemical nature of the degenerated tissue. With thionine it stains grayish blue, sometimes pinkish, but not a very deep color. With van Gieson's method it stains yellowish brown, sometimes reddish, but never intensely. In aniline blue sections it is an intense blue, sometimes containing yellowish patches. It stains faintly with eosin. In Bielschowsky preparations it is gray or black, and yellowish brown with tannin-silver. With

Fig. 7.—A large blood vessel of the white matter of the left brain hemisphere showing an early stage of hyalinization. Large masses of hyalin in the upper left part of the picture; pronounced glia activity in the lower part; infiltration around some of the smaller vessels. Nissl stain; × 50.

Fig. 8.—Severe hyaline degeneration of the pia vessels of the left cerebellar hemisphere. Infiltration of the pia-arachnoid (the lower part of the picture). Complete destruction of the granular layer and also of the Purkinje cells. The latter are replaced by "Strauchwerk." Nissl stain; × 50.

Spielmeyer's hematoxylin method it does not stain. Amyloid reactions are negative. In sudan III preparations it stains a pale yellow, showing little fat. The myelin remnants do not stain with sudan III. Fat is found in small quantities in several blood vessel walls, but the glial scar connective tissue and its degenerative products are free from fat.

Spinal Cord: Only changes of a secondary degenerative nature are found. They consist of shrinkage of the large ganglion cells and degeneration in the pyramidal tracts. In the cells the changes are severe, the tigroid substance is broken up and the nuclei are shrunken or not present at all. These same changes are seen throughout the gray matter of the different regions of the cord. Considerable gliosis is seen in both the left anterior and the right lateral pyramidal tracts. The changes of these tracts are best seen in Weigert sections, and it is noted that they extend throughout the length of the tracts. The blood vessels of the spinal cord show no changes such as are found in the brain and cerebellum.

COMMENT

As already mentioned, the literature contains sufficient pathologicoanatomic data to give a fairly well outlined picture of diffuse sclerosis. Except for a few observations in which unusual changes have been reported, one is dealing with different phases of myelin destruction and assimilation combined with more or less pronounced infiltrative phenomena, mostly confined to the blood vessel system.

We do not consider it necessary to review the literature on the subject, and refer to the excellent summaries of A. Jakob [2] and G. Steiner [6] which have been published recently. We restrict ourselves to commenting on the new and atypical points that we have observed. According to A. Jakob,[2] the diffuse sclerosis is characterized by the development of one or more foci that are restricted as a rule to the white matter and do not affect the fibrae arcuatae and gray matter or the configuration of the brain. This disease is in most cases, but not in all, symmetrical. The basal ganglia, the internal and external capsule, the anterior commissure, the pons and what is most important, the cerebellum, are frequently affected. The gray matter does not always escape. Small foci are most frequently found in it, but exceptions have been observed, and A. Jakob [2] reported an extensive destruction of the cortex.

The degeneration of the white matter is a regular and the most important pathologic change. Corresponding to the phase of the myelin destruction, most authors report tremendous masses of lipoids. The axis cylinders are, as a rule, rarefied, but persist much longer than the myelin.

These briefly summarized, most important histopathologic characteristics were practically all observed in our case. The myelin of both

6. Steiner, G., in Bumke: Handbuch des Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 2, pt. 7, p. 305.

forebrain and cerebellar hemispheres was destroyed over large areas; the deeper layers were entirely degenerated, whereas the U-fibers were relatively well preserved. The basal ganglia, the corpus callosum, the internal capsule and the anterior commissure were strongly affected; in the gray matter there are but few small foci. We have therefore sufficient reason to believe that the case belongs to the group in question.

Histologically, however, certain differences must be emphasized. We do not find the pictures of myelin degeneration given by practically all writers on this subject. Correspondingly, only a few scattered drops of lipoid are found in the blood vessel walls. The remains of the degenerated myelin that still can be traced are obviously so decomposed that they cannot be stained with sudan III. On the contrary, in the areas in which the myelin is still well preserved, no recent changes can be seen, and we get the impression that it is no longer being acted on.

Kaltenbach [3] described similar products of disintegration in his case. He found metachromatic products in tremendous amounts which stained violet or red with toluidine blue; they could be seen also with Kultschizky's stain as well as in fiber preparations; Alzheimer and Baranconi and Witte gave similar descriptions. Kaltenbach [3] could obtain partially positive scarlet red stains, whereas the microchemical characteristics in our case are somewhat different: As already mentioned, no positive fat stains were observed; toluidine blue and thionine furnished weak greenish pictures, and none was obtained with Weigert preparations. The most excellent results were observed in Mallory's aniline blue sections, in which the myelin remains appeared bright purple or deep yellow. With tannin-silver a deep brownish-yellow stain was obtained. It is interesting to note in this connection that Scholz [1] observed a similar microchemical behavior in a case of familial diffuse sclerosis in childhood: he could trace positive scarlet red products in blood vessel sheaths only.

Comparing all the microchemical data collected from the literature with our own observations, we conclude that we are dealing with a series of phenomena that show differences in degree and not in kind. All the cases in question belong obviously in one group. A. Jakob [2] regarded this mode of myelin disintegration as a special type of diffuse sclerosis.

The behavior of myelin in our case is of particular interest because its products of disintegration are present not only in the destroyed areas of the white matter but frequently also in the parenchyma and in the leptomeninges (chiefly in those of the cerebellum). This strange migration is made possible by widespread rarefaction of the parenchyma and the molecular layer. One has the impression that this strange process is not an active one but a stream of débris suspended in tissue fluid

which is no longer regulated by any physiologic mechanism and simply floods the rarefied tissue network and finally reaches the meninges. There is at the same time a hyaline degeneration of the blood vessels of the leptomeninges, and these two effects produce impressive histologic pictures.

The participation of the gray matter in diffuse sclerosis is not unusual. A. Jakob,[2] P. Schilder [7] and London and Frets [8] observed infiltrative phenomena in the leptomeninges, but none of these authors mentioned a migration of myelin into the latter or the rarefaction of the first layer as described by us.

The rarefaction of the first layer fits into the picture of the disease in question. Similar rarefaction has been described by Globus and Strauss [9] and others in the white matter. It is known in the literature as status spongiosus. The unusual feature lies again in the localization of this type of tissue destruction, and not in its nature; it is, however, sufficient to increase the histologic variation of our case.

Quite unusual, on the contrary, are the reparative phenomena, which, as we pointed out, are of a glial and connective tissue origin. The destroyed and digested myelin is first replaced by a dense glial scar. This scar remains completely passive and does not show signs of autonomous growth, nor does it penetrate the blood vessel sheaths or their lumen to affect the gray matter and the leptomeninges, but remains invariably restricted to the white matter of both the brain and cerebellum.

This peculiar glial production is perhaps related to several observations that are known in the neuropathologic literature as nonclassifiable. Outstanding among them is the observation of Hallerworden,[10] who described numerous symmetrical, indistinctly limited foci of demyelinization which neither reached the ventricle nor affected the gray matter, but could be seen in the basal ganglia, the internal capsule and the anterior commissure. The area of demyelinization contained an unusually large amount of glial elements. Among many different types, large blastomatous glia cells were observed. There was no zone of proliferation at the edge of the focus and the more advanced areas were poor in cells. The blood vessels remained unaffected and no inflammatory changes were present. Status spongiosus was seen in several places. Under the wall of the left ventricle there were two gliomas as large as lentils, neurinomatous in type and well defined.

7. Schilder, P.: Die Enzephalitis periaxialis diffusa, Arch. f. Psychiat. **21**: 527, 1924.

8. van Londen and Frets, G. P.: Psychiat. en Neurol. Bl. **30**:235, 1926.

9. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

10. Hallerworden, in Bumke: Handbuch des Geisteskrankheiten, Berlin, Julius Springer, 1928, vol. 2, pt. 7, p. 1063.

Hallerworden [10] interpreted his remarkable observations as a diffuse dysplasia of the glia which led to a blastomatous degeneration similar in type to tuberous sclerosis.

Probably there are certain relations between the observations of Hallerworden and those in our case, as we found also no tendency of dysplastic glia to affect the blood vessels, the gray matter and the meninges, and there was no proliferating zone at the edge of the glial scar. Again, we cannot interpret the glial dysplasia as a tumor growth in a strict sense, because of the peculiarity of its distribution: There were several separate foci in both hemispheres of the brain and cerebellum.

It is, however, doubtful whether we are dealing with the identical disease described by Hallerworden,[10] as we could not find a primary tumor formation, and there are considerable differences in the clinical pictures. Similar observations have also been reported by A. Jakob [11] and M. Bielschowsky,[12] and the last author calls attention to the similarity to von Recklinghausen's disease.

Whether we are dealing here with a congenital glial dysplasia or an unusual irritation of the tissue brought about by an unknown agent is histologically impossible to conclude, as there are but very few similar observations in the literature. Both possibilities should, however, be kept in mind.

This powerful and dense fiber network obviously places the already markedly irritated and swollen blood vessels under quite unusual conditions. The blood vessel elements proliferate and are swollen, and there is a heavy accumulation of lymphocytes and plasma cells. This tremendous irritation stimulates a highly effective connective tissue growth originating from the adventitia, by which the glial tissue is more and more replaced.

Connective tissue phenomena are as a rule observed in rarefied and disintegrated nerve structures, especially if the process of disintegration proceeds slowly. In our case all requisites for such reparation are at hand, as large areas of white matter have been undergoing a slow degeneration, and the blood vessels have withstood a constant irritation. In our opinion these factors account for the exceedingly pronounced connective tissue character of the reparation.

Hyaline degeneration, which sets in when the connective tissue organization is at its height, concludes the picture and brings the disease to an end. How does it originate? Our sections show clearly that the hyalinization begins invariably in the media of the blood vessels,

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11. Jakob, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:147, 1921.

12. Bielschowsky, M., and Rose, M.: Zur Kenntnis der zentralen Veränderungen bei Recklinghausencher Krankheit, J. f. Psychiat. u. Neurol. **35**:42, 1927.

destroys the myofibrils, advances into the intima and adventitia, spreads finally into the connective tissue fibers and destroys in this way large parts of the scar. As we have already said, the hyalinization is restricted to the connective tissue elements only, and never appears primarily in glial structures or cells. These suffer purely accidentally: Surrounded by large hyaline masses and deprived of nourishment, they degenerate and disappear completely and the meshes are filled up with transparent masses of hyalin. This is an observation that has never before been described in diffuse sclerosis, and was not mentioned by Hallerworden in his observations.

We are using the term hyalin and not colloid for the following reason: The hyalin always appears in connective tissue and not in the glia or other elements; it is a classic example of a connective tissue product, whereas colloid is reserved for the description of epithelial cell products (colloid of the thyroid or of cancers). We realize, however, that the term hyalin is applied to describe many different transparent pathologic materials, and reveals nothing as to their chemical nature.

The histopathologic picture is still more complicated by the hyaline degeneration of the leptomeninges and the blood vessels, for which no responsible conditions could be discovered. As there are no dysplastic phenomena in the leptomeninges, it is obvious that the interpretation given for the destruction of the white matter is not sufficient for that in the meninges, and the same is true for the gray matter.

We wish to call attention to one interesting symptom: This is the destruction of the first layer and the limiting membrane as an expression of a complete destruction of the meningovascular barrier, not previously described.

Reviewing the almost inexhaustible histologic details, one is at a loss as to the classification. As pointed out, there is a very considerable conformity with diffuse sclerosis; the pronounced dysplasia of the glia with perhaps some blastomatous tendencies, pronounced inflammatory changes on one side and widespread degeneration on the other, makes a clear classification so far impossible, and we have chosen, therefore, the name atypical diffuse sclerosis as that of the most closely related group histologically.

The clinical course is characterized by the chronicity of the disease and pronounced muscular atrophies. Unfortunately, the clinical record does not specify the distribution of the atrophies or the muscle groups involved, and does not contain the exact neurologic status. We do not know anything about pyramidal symptoms, which were very likely present as the Weigert sections of the spinal cord suggest. On the other hand, a number of symptoms, such as epileptic seizures and mental changes, do not clarify the clinical picture, and such important symptoms as blindness and deafness were altogether absent. We are there-

fore much restricted in our clinical considerations, but we doubt whether a clinical diagnosis would have been possible even under different circumstances.

SUMMARY

1. A peculiar mental disease of approximately eleven years' duration associated with progressive muscle atrophies is described.

2. Pathologico-anatomically, the most outstanding feature is a destruction of the white matter in both cerebral and cerebellar hemispheres without distortion of the brain.

3. The destroyed myelin is replaced by peculiar glial tissue, which in the later stages is penetrated by connective tissue fibers and finally undergoes hyaline degeneration.

4. The cortical gray matter is only occasionally, and the cerebellar parenchyma very severely, affected.

5. The leptomeninges of the cerebellum are in many places hyalinized, and the meningovascular barrier is broken down.

6. The relation of the case to diffuse sclerosis and dysplastic disturbances of the glia is discussed.

HYDROCEPHALUS

REPORT OF A CASE IN AN INFANT WITH VESTIGES OF A CHOROID PLEXUS IN THE FOURTH VENTRICLE ONLY *

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Elsewhere,[1] instances have been presented of a vast accumulation of fluids in the cerebral ventricles (hydrocephalus) in the presence of defective choroid plexuses. In practically all my cases of hydrocephalus, as well as in the majority of those gathered from the literature, the choroid plexus was atrophied, buried or encased, as it were, within the walls of the ventricles, and thus rendered practically functionless. One may argue that much as the choroid plexuses were reduced, the remnants might have sufficed to function and supposedly secrete cerebrospinal fluid.

Such bare possibilities were lacking in the case to be described. A huge hydrocephalus was present; yet not even traces of a choroid plexus in the lateral or third ventricles could be made out. The third ventricle was obliterated by an inflammatory process and thus completely isolated the lateral ventricles which, as said, were enormously dilated by the cerebrospinal fluid.

REPORT OF A CASE

A white boy, born by normal delivery in the Research Hospital of the University of Illinois on Jan. 16, 1930, exhibited over the dorsolumbar region of the spine a tumor mass about 4.5 cm. in diameter, "over which there was no skin." Examination revealed the mass to be a meningomyelocele; the fontanels (anterior and posterior) were open, large and bulging, and the sutures were separated.

Course.—The bulging of the fontanels grew progressively larger. About three days after birth, some leaking was noticed from the lower "part of spine." The discharge became purulent (on February 5); the temperature was usually elevated; the child lost weight; he took nourishment poorly; the stools contained large

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* From the Pathologic Laboratories of the Research and Educational Hospitals, University of Illinois, and the State Psychopathic Institute.

* Read by title at the Fifty-Seventh Annual Meeting of the American Neurological Association, Boston, May 29, 1931.

1. Hassin, G. B.: Hydrocephalus; Studies of the Pathology and Pathogenesis, with Remarks on the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **24**:1164 (Dec.) 1930.

quantities of mucus (hunger stools), and the abdomen was distended. Within the next few days, the lower extremities became paralyzed, but sensibility was preserved. On February 13, the meningocele was punctured and slowly yielded 0.5 cc. of a yellow fluid. Cultures from this fluid showed Staphylococcus albus. It contained many red and white cells, and turned into a "yellowish coagulum." The temperature of the child was 101.2 F., and the discharge from the meningocele was purulent.

A spinal puncture February 14 yielded a turbid fluid that was yellowish; the cell content was similar to that of the fluid removed on February 13 from the meningocele. The fluid obtained from the ventricles was of a "yellowish tint, clear, contained 66 cells per cubic millimeter, had a markedly strong Pandy reaction and a negative Ross Jones reaction." The colloidal gold curve of this fluid was "negative." A cisternal puncture was attempted but was unsuccessful.

The head grew steadily larger; on February 22, the circumference was 40.5 cm.; on March 5, 42; on March 10, 43; on March 26, 44.3, and on April 3, 45 cm. On March 15, a "profuse nasal discharge" appeared and was followed by discharge from the ear and nose. In spite of so many threatening signs, there was a short remission. A note made on March 29 reads: "the head is larger; the gastrointestinal condition and metabolism are excellent; the weight has increased; the otitis media has ruptured."

During the following days, however, the condition became worse. The temperature rose to 104 F.; the extremities exhibited anesthesia; the meningocele became eroded in several places, and "pressure on the lower edge of the sac produced twitchings of the legs."

On April 10, twitchings appeared also in the left arm and leg; the eyes had been "discharging"; signs of bronchopneumonia appeared, and the child died on April 11, with a temperature of 107 F.

Laboratory Studies.—Examination of the blood revealed: hemoglobin from 90 to 95 per cent; red cells, 4,100,000; white cells, 18,950, of which 34 per cent were lymphocytes, 40 per cent polymorphonuclears and 6 per cent eosinophils. Examination of the urine gave negative results. The spinal fluid gave a negative reaction to the Wassermann test, and, as mentioned, yielded on culture Staphylococcus albus. The differential count of cells in the fluid showed a predominance of polymorphonuclear cells and an absence of gram-positive micro-organisms. The Giemsa stain furnished no information.

Roentgenograms revealed a mild hydrocephalus and a spina bifida. A Wassermann test of the blood was not made.

The clinical observations were summarized as spina bifida (meningomyelocele) of the upper lumbar region; hydrocephalus; purulent ventricular fluid containing Staphylococcus albus and a seropurulent discharge from the ruptured and eroded meningocele.

Necropsy (Dr. Milles).—Some of the prominent changes were: huge hydrocephalus; spina bifida over the spinal column, from the ninth thoracic to the fourth lumbar vertebra, in the form of a tumor mass, 4 cm. in diameter; its central portion was represented by a "thin membrane covering a gelatin-like substance surrounded by an opaque margin." The cranium was very thin and in some areas was of almost "paper consistency." The convolutions of the brain were flattened; the parenchyma was reduced to a thin film of tissue and when the fluid escaped the brain collapsed. The fluid contained many flakelike particles.

The cord appeared normal; at the lower level of the thoracic portion it discontinued abruptly and was replaced by the tumor mass as already described. Dissection revealed that the spinal canal was closed by a fibrous membrane.

Additional observations of the brain, after it was delivered to my laboratory in a solution of formaldehyde, revealed: a protrusion of the occipital lobe which extended over a well preserved cerebellum; greatly dilated ventricles; a patent sylvian aqueduct; a gelatin-like mass within the ventricles (fig. 1), forming their inner lining, and an absence of the choroid plexuses in the lateral ventricles. Some portions of the brain collapsed, the opposite walls, as the picture shows, being

Fig. 1.—The gelatin-like masses within the ventricles are well shown, especially in the lower blocks at G.

in close contact and separated from one another by a thin layer of gelatin-like substance. The fourth ventricle was also somewhat reduced in size, and through its open Luschka's recesses a portion of the choroidal tela, with a thin strand of the choroid plexus, was protruding. The corpus callosum was much thinned, and the linings of the ventricles, when they were not covered by the gelatinous mass, were thickened, soft and granular. The caudate and lenticular nuclei could not be discerned.

Microscopic Observations.—The architecture of the cerebral cortex was well preserved; that is, the cortical lamellation was nowhere affected. The deep strata bordering on the dilated ventricles were represented by a gelatin-like, colloid substance. It was separated from the preserved subcortex by several layers of cells, bordered above by masses of blood vessels which were densely enveloped by collars of plasma cells (fig. 2).

Fig. 2.—The destroyed ependyma and subependymal areas. The upper part in the picture is vacuolated, the vacuoles being preameboid glia or so-called swollen oligodendroglia. The base, at *A*, is covered by dense foci of polymorphonuclear cells mixed with other cells described in the text; at *B* is the layer of macrophages mixed with gitter cells, and above, at *C*, is the layer of infiltrated blood vessels. This layer with the subjacent layer forms in scarlet red specimens a broad layer of lipoids seen in figure 4. Toluidine blue; × 56.

The gelatin-like layer in some places was covered by cell bodies, polymorphonuclear leukocytes, occasional plasma cells, macrophages and a few gitter cells filled with fat (fig. 3). The gitter cells and macrophages predominated in the next zone (fig. 4), where the former appeared especially numerous, while the macro-

phages, which were of huge size, were filled with broken-up cells and nuclei. The superjacent zone consisted of dense layers of plasma cells, some of which were of unusually large size, real giant cells, often containing two nuclei with a distinct halo. They were also scattered over the tissues singly and occurred as dense muffs around the blood vessels (figs. 2 and 5). The latter exhibited unusually well developed and enormously infiltrated (fig. 5) walls (mainly plasma cells) in which masses of a gelatin-like substance were also much in evidence. In some instances the walls of the blood vessels showed regressive phenomena. They were reduced to a mere membrana elastica, while in other cases again the walls consisted of hypertrophied adventitial and endothelial cells.

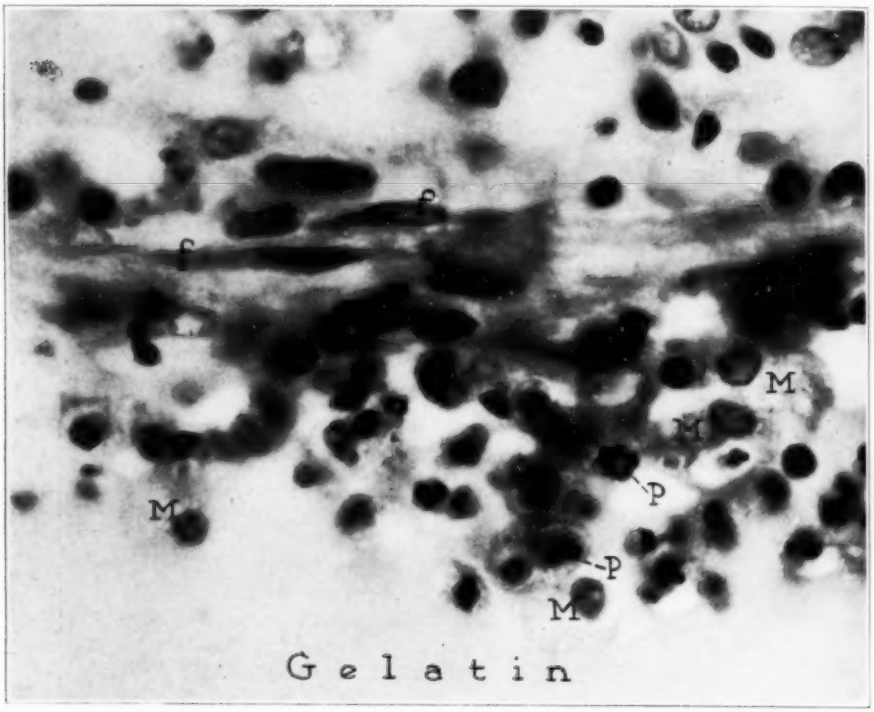

Fig. 3.—At the bottom, the ependyma is replaced by gelatin-like substance covered with polymorphonuclear cells (*P*), some within macrophages (*M*) bordered above by large fibroblasts (*f*). Van Gieson's stain; × 900.

The zone of blood vessels infiltrated with plasma cells bordered on the subcortical white substance, which, in areas particularly affected, exhibited enormous amounts of preameboid glia cells or so-called swollen oligodendroglia. They gave (fig. 6) the field a sievelike vacuolated appearance; their nuclei often showed karyolysis—broken-up chromatin which gathered as minute granules at the periphery of the nucleus. Some glial formations were of the ameboid type: The nuclei were densely stained and pyknotic, and possessed abundant homogeneous, rather pale cytoplasm with the nucleus misplaced to the periphery. Other cells were preameboid or, as they have of late often been called, swollen oligodendroglia. Their nuclei, rich in chromatin, were surrounded by rings bridged by processes emanat-

ing from the nucleus. In a few instances, these cells resembled cytoplasmic glia cells, their processes radically extending from the shrunken cell body to the surrounding tissue, of which they formed an inseparable part. Such cells could be seen especially well in specimens stained with the method of Alzheimer-Mann. The foregoing glial changes, the majority of which were of regressive nature, were present mainly near or within the affected area. In areas near the cortex, other glial changes of a progressive character, so-called cytoplasmic glia cells, were prevalent. Their nuclei were rich in chromatin, and the cytoplasm was abundant and branching. These cells were intermingled with sausage-like cell bodies or rod cells (microglia); they were not only rich in chromatin, but were well provided with

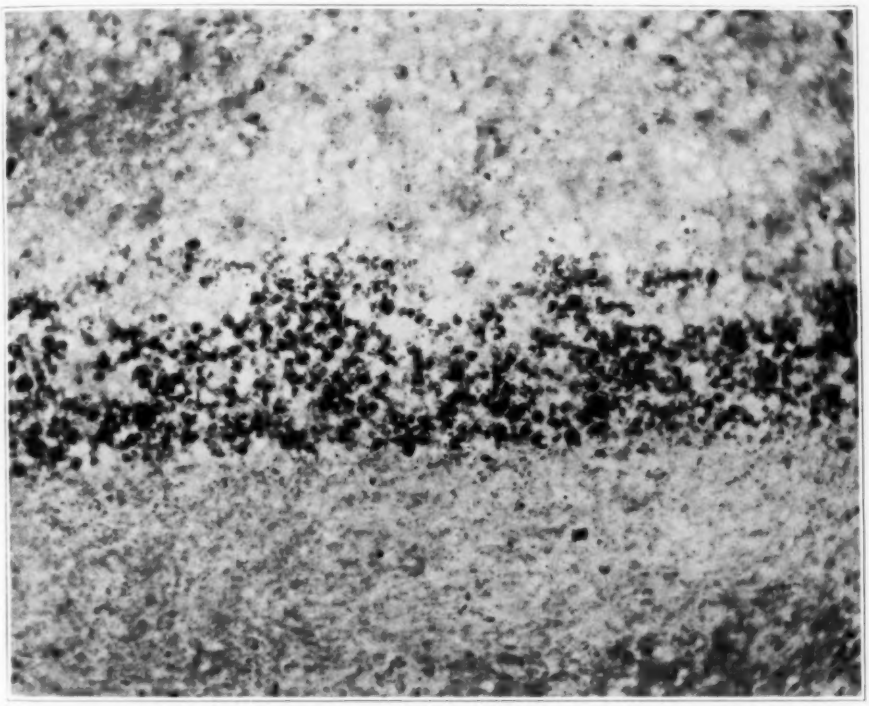

Fig. 4.—The broad zone of the gitter cells and infiltrated blood vessels is seen dividing the lower subependymal and ependymal areas from the better preserved sievelike area above. Herxheimer stain; × 140.

processes at the poles; often they contained vacuoles, and the nuclei appeared kidney-shaped.

The ganglion cells themselves were throughout profoundly changed, and the subcortical layer in many places appeared rarefied. The former were disintegrated, broken-up, vacuolated and often homogeneous. The nuclei also were homogeneous and poor in chromatin, and the processes were well and diffusely stained, thinned and tortuous. In the cornu ammonis the ganglion cell destruction was most severe. In many instances the ganglion cells were represented by pale nuclei, practically devoid of chromatin; the cytoplasm was liquefied and filled with cavities, which were often invaded by neuronophages. Some ganglion cells

showed a marked shrinkage and were corkscrew-like; when stained with the silver method of Stöhr-Schultze these cells were covered with granules, especially at the margins. The ganglion cells then appeared as if incrusted with silver. The nerve fibers in the white substance, stained with the same method, were tumefied, fusiform, irregular in shape and often broken up.

The cerebellum exhibited much milder changes, but the Purkinje cells were swollen, and their tumefied, well-stained processes densely covered the molecular layer.

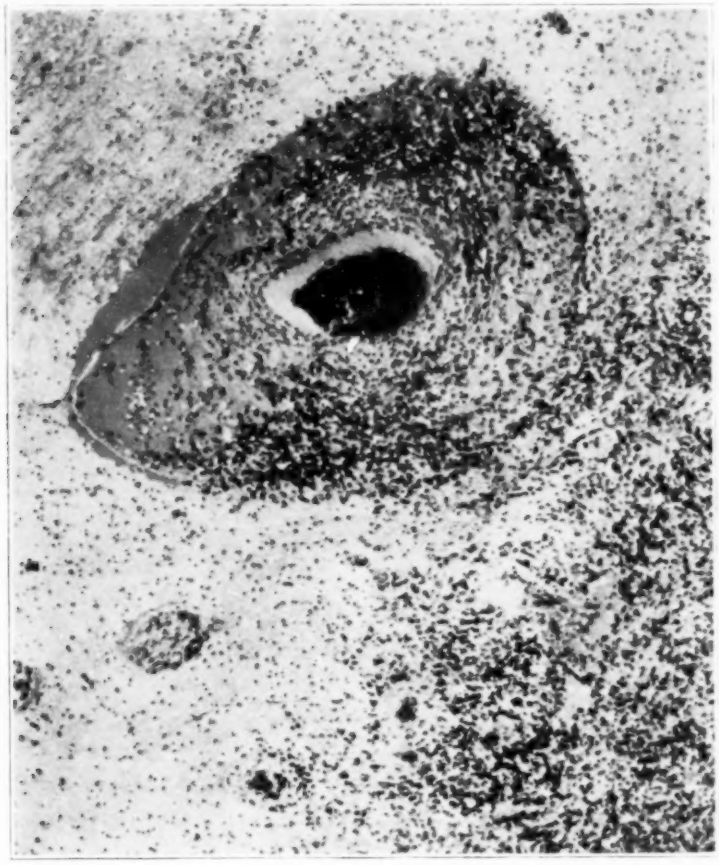

Fig. 5.—An infiltrated blood vessel and the gelatin-like masses described in the text. Van Gieson's stain; × 80.

Like the rest of the brain, the cerebellum was carefully studied for fat changes. No lipoids were found in the cerebellum, but they were present in large masses in some ganglion cells of the brain; large amounts were present also in the marginal ventricular zone between the gelatin-like substance and the preserved brain tissue (fig. 4). In the brain tissue proper, minute fat granules were also scattered in the glia nuclei and within the lumens of some larger blood vessels, where they often obscured the blood cells.

The pia-arachnoid was hyperplastic throughout, especially at the base of the brain. The arachnoid trabeculae were also thickened and covered by distinct spindle-shaped mesothelial cells. The latter were numerous and were mixed with macrophages and gitter cells. There were also present polyblasts and fibroblasts, and often particles of an amorphous gelatin-like substance were found, especially in the cerebellar pia-arachnoid. The blood vessels of the pia were hyperemic and not infiltrated, and in general appeared normal.

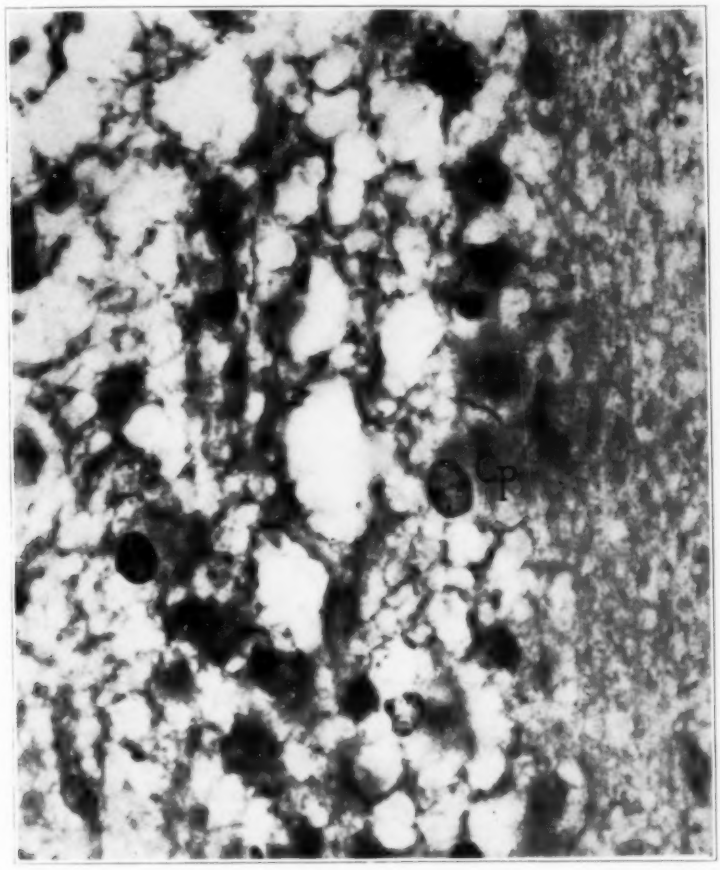

Fig. 6.—Foci of rarefaction with large cytoplasmic glia cells (*Cp*). Van Gieson's stain; × 900.

The Choroid Plexus, Third and Fourth Ventricles.—As has been pointed out, no traces of a choroid plexus were in evidence in the lateral ventricles; no ependyma was discerned here either. The latter was replaced by thick degenerated masses already described and illustrated in figures 1 and 2. The third ventricle was likewise profoundly changed. As figure 7 shows, it was filled with a cellular mass consisting of plasma cells. No polymorphonuclear cells were among them. The ependyma was well developed and bulging (fig. 7 *Ep.*) and formed a sharp contrast between the appearance of the third ventricle and that of the surrounding

tissues. In the latter, however, plasma cells were not uncommonly intermingled with numerous cytoplasmic glia cells.

The sylvian aqueduct (fig. 8), in contrast to the third ventricle, was patent or partially obstructed, was filled mainly with gitter cells, and showed no ependymal changes. The fourth ventricle was likewise open and, as figure 9 shows, contained remnants of the choroid plexus. This, possessing very few tufts, was in the form of digits consisting of fibrous connective tissue covered with epithelial cells. The

Fig. 7.—The third ventricle dilated, packed with masses of hematogenous cells, and divided from the surrounding pale cerebral tissue by a well defined ependyma (*Ep*). The large round masses below are the red nuclei. Van Gieson's stain; × 17.

latter possessed a homogeneous cytoplasm without vacuoles and a dark nucleus, rich in chromatin. Blood vessels were absent throughout, in the tufts as well as in the stroma of the choroid plexus. Over some tufts the epithelial covering was discontinuous and broken up, and the cytoplasm appeared fragmented. In other places, the tuft cells were enveloped by proliferated connective tissue, which formed over them a dense scar. In short, the choroid plexus was transformed into an

avascular mass of connective tissue, which was covered with various nuclei. Some cells were fibroblasts, containing oblong, oval or large nuclei with processes from the poles; some were polyblasts, with curved nuclei, poor in chromatin and situated within an abundant cytoplasm, while others appeared as lymphocytes.

The spinal cord was not available for study.

Summary of the Clinical and Pathologic Observations.—In an infant born with a spina bifida, a manifest hydrocephalus developed about one

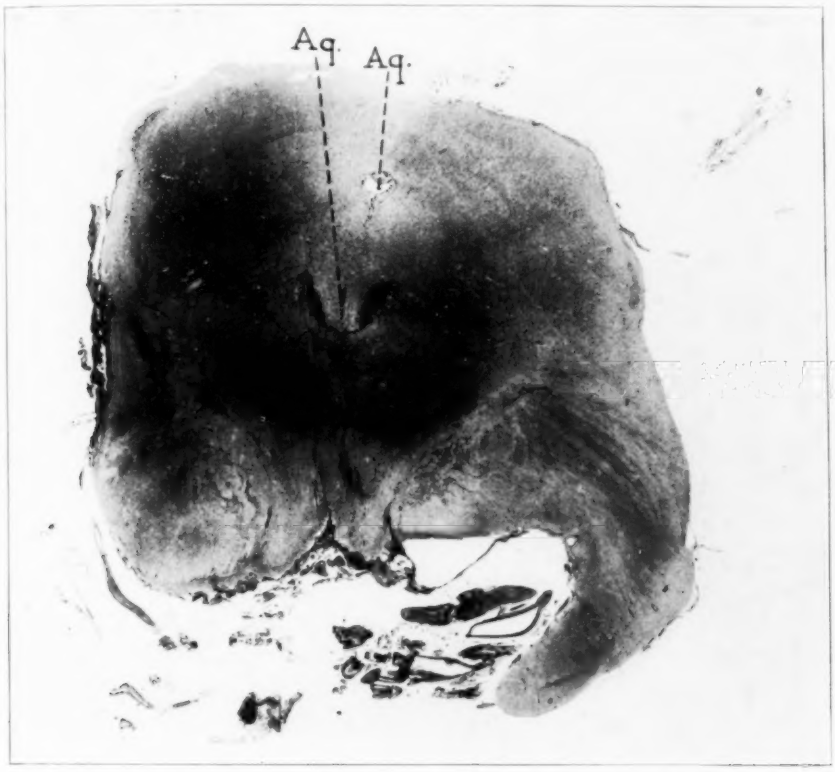

Fig. 8.—The sylvian aqueduct (*Aq.*) is patent. Van Gieson's stain; × 80.

month later, and death from sepsis occurred. Pathologic observations revealed: Replacement of the ependyma by a gelatinous mass, which partly filled the greatly dilated ventricles; an absence of the choroid plexuses in the lateral and third ventricles; occlusion of the third ventricle, and fibrosed remnants of a choroid plexus in the fourth ventricle.

COMMENT

Like any other case of hydrocephalus, the one here recorded was secondary to an obstruction, which here was in the third ventricle.

The fluid from the lateral ventricles thus could not escape through the sylvian aqueduct to the fourth ventricle to be discharged through the recesses of Luschka. It was isolated within the lateral ventricles, giving rise to a hydrocephalus. In some histopathologic features, this case differs from those recorded elsewhere.[1] The differences to be noted are: a comparatively mild external hydrocephalus; a less diffuse rarefaction

Fig. 9.—The choroid plexus of the fourth ventricle is represented by digits, many of which are encased in fibrous connective tissue. Van Gieson's stain; × 80.

of the cerebral tissues, which was here of a more local nature; more advanced parenchymatous changes, and above all a destruction of the ependymal and subependymal tissues with transformation of a part of them into a gelatin-like colloid substance. The differences were for the most part due to the etiologic factor, a suppurative inflammation of the inner lining of the ependyma (ependymitis). This was responsible

for the degeneration of both the ependymal and the subependymal tissues and for the so-called toxic parenchymatous changes that have been so well described in the brains of animals by Lotmar,[2] and in human material by Low.[3] The enormous accumulation of polymorphonuclear cells over the colloid mass in the lower layers of the brain and their lack in the upper strata are also of significance. This shows that the contents of the cerebral ventricles, as a rule, do not invade the cerebral parenchyma, but may do so under pathologic conditions, although only for a short distance. In normal conditions, the currents of the tissue fluids within the Virchow-Robin spaces are from the brain toward the ventricles and not from the latter to the brain. For this reason, it is suggested that the vast accumulation of ventricular fluid in the case reported in this paper was the result of discharge of tissue fluids from the brain. The fluid could not have been produced by the choroid plexus, for none was present in this case. If one grants that it existed, and that, like the ependyma, it became destroyed by a pathologic process, its destruction could not have taken place abruptly. It certainly required weeks, during which the choroid plexus evidently was badly affected. Yet the ventricular fluid kept on accumulating, as is evidenced by the size of the head, which was steadily increasing. Were the choroid plexus an organ of secretion, such a vast accumulation of fluid could not have taken place in this case with the choroid plexus badly affected. A somewhat similar situation has been realized by others. Merle,[4] for instance, ascribed the excessive formation of ventricular fluid to an inflammation of the ependyma, an ependymitis. In my case, however, the ependyma, like the choroid plexus, was destroyed; its lesion, like that of the hydrocephalus, was secondary to the obstruction of the third ventricle.

According to numerous pathologic data repeatedly discussed,[5] the choroid plexus is an organ of excretion and of absorption of some constituents of the cerebrospinal fluid which it renders harmless and absorbable. In this case, which was observed first in an obstetric and later in a pediatric ward, the ventricular fluid could not be studied from

2. Lotmar, F.: Beiträge zur Histologie der acuten Myelitis und Encephalitis, sowie verwandter Prozesse, in Nissl and Alzheimer: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, Gustav Fischer, 1913, vol. 6, p. 145.

3. Low, A. A.: Acute Toxic (Nonsuppurative) Encephalitis in Children, Arch. Neurol. & Psychiat. **23**:696 (April) 1930.

4. Merle, P.: Étude sur les épendymites célébrales, Thèse de Paris, 1910.

5. Hassin, G. B.: Notes on the Nature and Origin of the Cerebrospinal Fluid, J. Nerv. & Ment. Dis. **59**:113 (Feb.) 1924; Effect of Organic Brain and Spinal Cord Changes on Subarachnoid Space, Choroid Plexus and Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **14**:468 (Oct.) 1925.

all angles of biochemistry, but it did show abnormal changes (a high cell content and an abnormal color, and it coagulated quickly). It was an abnormal fluid, undoubtedly responsible for the gelatinous appearance of the ventricular contents (fig. 1) and the degeneration of the ependyma. When the homogeneous contents, pictured in figure 1, were examined, one gained the impression that they turned into a gelatinous mass by a process of hardening. A similar mass was present also within the brain tissue (figs. 3 and 5). It formed (fig. 5) a part of the periadventitial infiltration masses, extending over the detached adventitia. The mass was covered by numerous hematogenous elements (especially to the right of the picture). In smaller amounts it could be seen outside the blood vessel (in the right lower corner), where it was somewhat obscured by masses of cell elements. The gelatinous masses here were most likely tissue fluids of the brain that had become stagnant, for they could not be discharged by way of the Virchow-Robin spaces either into the ventricles or into the subarachnoid space. In cases of hydrocephalus in which remnants of choroid plexus were present such phenomena of abnormal stagnant cerebral fluids were not observed. The case reported here thus gives an approximate idea of what may happen to a brain that is deprived of a choroid plexus.

The condition of the choroid plexus in the fourth ventricle, which was fibrosed and transformed into an actual connective tissue scar, is also of great significance. No signs of suppurative inflammation were here in evidence; the ependyma and subependymal tissues were not affected; the majority of the tufts were encased in foci of connective tissue, those remaining being covered by homogeneous or fragmented cells containing an equally homogeneous pyknotic nucleus. It is not possible to give an adequate explanation for such a choroid plexus. Whether it was a reaction to an adjacent condition or an atrophy from "disuse," I am unable to say; more cases of obstruction of the midbrain must be studied.

A number of other problems are suggested by this remarkable case: the spina bifida itself; the mode of invasion of the ventricles by an infection, whether it came partly from the spinal cord or whether it was caused entirely by a direct infection of the ventricles following puncture; the absence of a basilar or surface meningitis (external meningitis) in the presence of a very severe internal suppuration, and the condition of the perineurial spaces of the brain and spinal cord. Fortunately, these problems, which could not be studied for various reasons, are of secondary importance when compared with the problems pertaining to the relationship between hydrocephalus and an absence of choroid plexus.

CONCLUSIONS

1. Hydrocephalus may occur not only in cases in which the choroid plexus is deficient, but also in those in which it is entirely obliterated by an infectious process.

2. The histologic changes in such cases of hydrocephalus may differ somewhat from those in ordinary cases in which the cause of the obstruction is at the base of the brain.

3. Hydrocephalus was associated with marked ependymal and subependymal lesions which were not the cause of the hydrocephalus, but, like the latter, were due to an obstruction.

4. Such cases furnish additional proof that the spinal fluid does not originate from the choroid plexus.

Clinical Notes

INTRAMEDULLARY TUMOR OF THE SPINAL CORD AND A VASCULAR LESION OF THE CEREBRUM *

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The purpose of this paper is to report certain procedures employed in the differential diagnosis of neurologic lesions in the case of a man with outstanding symptoms of pain and incoordination of the right hand, on which right hemiplegia was superimposed.

REPORT OF CASE

Clinical History.—A man, aged 52, came to the Mayo Clinic on Oct. 22, 1930, with a complaint of pain, of ten years' duration, in the right upper extremity. Pain of unknown etiology had been present in the back of the neck for nine years. For a year, this pain had remained bilateral and then gradually extended from the right side of the neck and head down the right arm; the hand became involved five years after the onset. The radial side of the forearm and hand was affected first. The pain recurred at intervals of from four to twelve months, lasted from three to six weeks, and consisted of sharp, lightning-like stabs which started in the right side of the neck and head and extended peripherally. In each interval the patient was entirely free from pain. For the last five years, pain had been continuous in the right upper extremity. It was described as a gnawing ache and was most severe in the hand. Temporary relief could be obtained by the administration of drugs. Occasionally, as much as 20 or 25 grains of amytal would be taken in twenty-four hours. Six months after the onset of pain, numbness and prickling commenced in the back of the neck; these gradually became worse, and spread slowly down the extremity, involving the hand eight years later. Two years after the onset, the presence of slight incoordination became apparent in the patient's writing, and three years later he had to write with his left hand. Loss of strength accompanied the incoordination, and all the muscles of the extremity became atrophied. In January, 1930, while at work, he had a severe attack of sneezing. He suddenly felt unwell, walked to a chair, and in fifteen minutes sank into unconsciousness that lasted for twelve hours; this was not accompanied by stertorous breathing, convulsion or muscular spasm. The patient was then able to talk but

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* From the Section on Neurologic Surgery, the Mayo Clinic.

was irrational for two days. Slight facial weakness was thought to be present at that time, and since then there had been a partial right hemiplegia, with difficulty in finding the right word at times. He was confined to bed for a few days and was then able to walk with the aid of a cane. Various therapeutic measures had been tried, including extraction of teeth, tonsillectomy and removal of the superior and middle cervical sympathetic ganglia of the right side. The patient had not derived benefit from any of these measures.

Examination.—The patient was fairly well developed, was 5 feet, 9 inches in height (175.3 cm.), and weighed 135 pounds (61.2 Kg.). The systolic blood pressure was 110 and the distalic 80 mm. of mercury; the pulse rate and the temperature were normal. The Wassermann test of the blood and other labora-

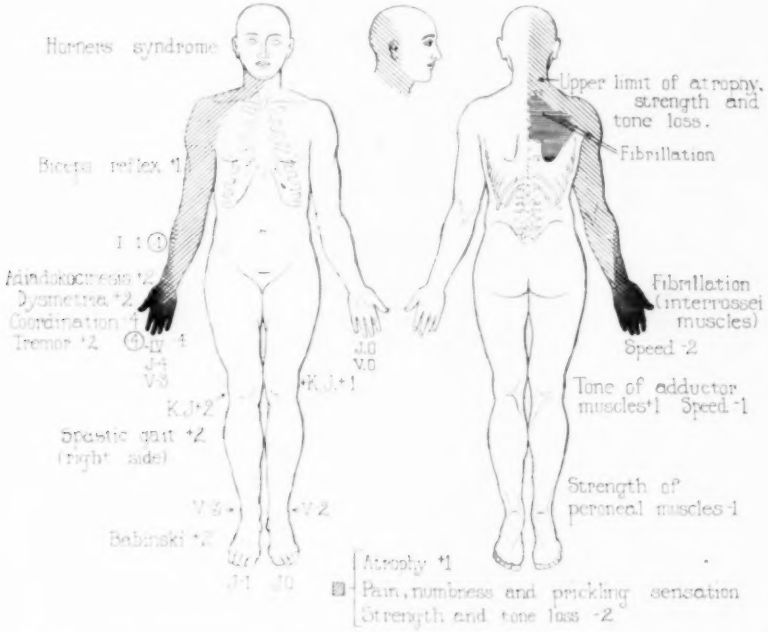

Fig. 1.—The neurologic data. The intensity of changes is charted on a basis of *0* to *4*. *0* indicates normal; *—4*, absence; *+4*, the most intense. When a numeral only is present, the Arabic represents appreciation of touch; the encircled Arabic, pain, and the Roman, temperature.

tory tests gave negative results, and roentgenograms of the thorax and cervical spine were normal.

The most striking feature was the disability of the right hand. Besides the pain, incoordination graded 4, adiadokokinesis and dysmetria (fig. 1) were noted. Sensation to touch, painful stimuli and temperature was graded —4 at the finger tips, gradually changing to normal at the elbow and on the ulnar side of the forearm. The muscles of the extremity, including those of the shoulder girdle, were atrophied, graded 1. There were also a loss of strength and tonus and a decrease of speed, as indicated by the finger wiggle; each was graded —2. Slight fibrillary twitching in the region of the scapular and rhomboid muscles and

coarser twitching in the interosseal muscles were noted. The right biceps reflex was greater than that of the left. Vibratory and joint senses were reduced, and there was tremor, graded 2. The tonus of the adductor muscles in the right thigh was increased, graded 1, and speed was slightly reduced. The strength of the peroneal group was decreased, graded 1. Vibratory sense, decreased in both lower extremities, was more marked on the right. The patellar reflexes were hyperactive, the right being increased more than the left, and there was a positive Babinski sign on the right. The gait also was slightly spastic on this side. Horner's syndrome was present on the right, a result of right cervical sympathectomy. Manometric readings of the cerebrospinal fluid revealed a pressure of 2 cm., which decreased to 0 after 5 cc. of fluid had been removed. The response to jugular pressure was slightly delayed. The fluid removed was clear, had a total protein content of 60 mg. per hundred cubic centimeters and 1 small lymphocyte for each cubic millimeter. The gold curve was not of pathologic significance.

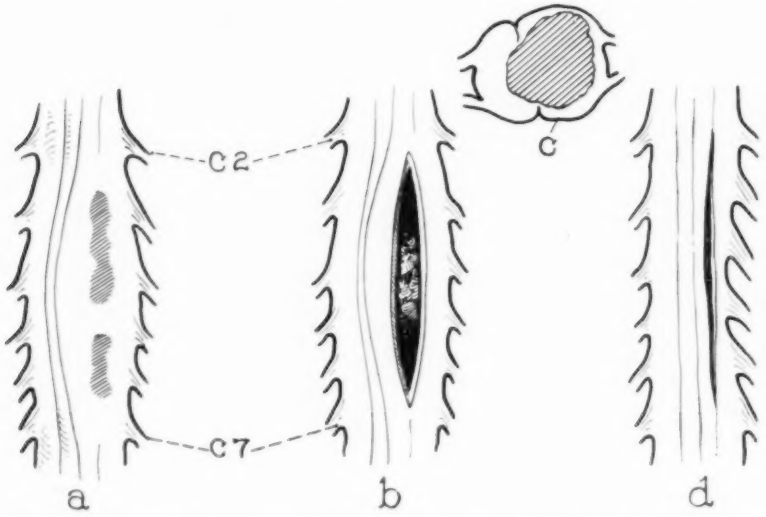

Fig. 2.—Intramedullary tumor of the cervical portion of the spinal cord, posterior view. In *a*, the shaded portions represent bluish cystic areas in the right dorsolateral region; *b*, shows the tumor area incised, cystic fluid evacuated, and the tumor showing at the level of the third to the fifth segment; *c* is a cross-section, showing the amount of cord involved, and *d* shows the operation completed, with the cavity left open.

Diagnosis.—The problem in the diagnosis was to decide whether there was a lesion of the cervical portion of the spinal cord, an intracranial lesion, or a lesion of the cervical portion of the spinal cord with a superimposed lesion of the cerebrum. In favor of a lesion of the cervical cord were: (1) the onset of pain, which remained localized to the area of distribution of the cervical nerves; (2) monoplegia, including incoordination, adiadokokinesis, dysmetria, fibrillary twitching, tremor, reduction of speed, atrophy and sensory changes; (3) the existence of monoplegia for a number of years before apoplexy occurred; (4) monoplegia,

with superimposed hemiplegia, which persisted after recovery from apoplexy, and (5) a delayed response to jugular pressure and a slight increase in the amount of protein in the spinal fluid.

The presence of localized fibrillary twitching, in addition to signs of tumor of the spinal cord, are indicative of an intramedullary lesion. However, the presence of pain preceding other symptoms and signs is usually found with extradural tumors. Syringomyelia must also be considered in the diagnosis. In this condition there may be a central type of pain, but with a history of pain for ten years one would expect to find the usual dissociated type of anesthesia and evidence of trophic changes. Against a diagnosis of causalgia are the type and distribution of the pain, the lack of history of injury and the presence of positive signs of a cord lesion. In favor of a thalamic lesion followed by a cerebral vascular accident were the character of the pain, the anesthesia with loss of joint sense and overreaction to painful stimuli, followed by apoplexy and signs of hemiplegia. Against

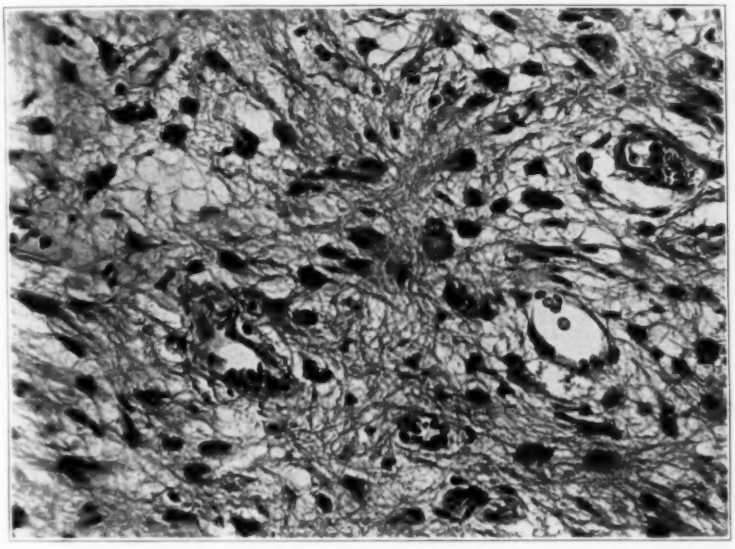

Fig. 3.—Photomicrograph of a section from the astrocytoma. Fibrillary and protoplasmic types of cells are present.

this diagnosis were the localized signs in the right hand and arm for many years preceding apoplexy.

Encephalography.—Considering the possibility of a lesion of the cervical portion of the spinal cord and a lesion in the cranium, encephalography in combination with the injection of iodized poppy seed oil 40 per cent was carried out. Sixty cubic centimeters of fluid was removed by cisternal puncture, and 55 cc. of air was injected by the fractional method; 5 cc. of iodized oil was then introduced through the same needle. Encephalography revealed enlarged sulci and slight convolutional atrophy over the left cerebral hemisphere, indicating that the hemiplegia was intracranial in origin rather than dependent on a possible lesion of the spinal cord. The study with iodized oil revealed a filling defect consisting of

evidence of division of the column of iodized oil in the spinal canal between the third and fifth cervical vertebrae. This suggested an intramedullary tumor or cyst of the cord. The results gave conclusive evidence of the existence of two pathologic conditions, namely, an intracranial lesion which, in view of the history, was probably of vascular origin, and a lesion of the cervical portion of the spinal cord.

Which of the two lesions caused the pain remained to be determined. In order to rule out pain of central origin due to a thalamic lesion, 150 mg. of procaine hydrochloride was injected into the spinal canal between the twelfth dorsal and the first lumbar vertebra. Following this injection, anesthesia developed up to the first thoracic segment and analgesia developed as high as the second cervical nerve, which promptly diminished the pain in the patient's right hand. This suggested that the lesion producing the pain was situated in the cervical portion of the spinal cord. In view of the observations on spinal puncture and the relief that resulted from spinal anesthesia, laminectomy was advised for the purpose of exploring the cord and sectioning the sensory roots if it was not possible to remove a tumor.

Laminectomy.—The operation was performed under local infiltration and paravertebral anesthesia, after a preliminary injection of ⅛ grain (0.008 Gm.) of morphine sulphate and 1/200 grain (0.003 Gm.) of scopolamine hydrobromide. The spinal dura was exposed by right unilateral laminectomy, which extended from the second cervical to the second thoracic vertebra. When the dura was opened, pale bluish areas appeared in the cord between the third and seventh cervical segments on the right dorsolateral surface (fig. 2), and a distinct mass could be palpated in the cord between the cystic areas opposite the fourth and fifth cervical roots. About 5 cc. of yellow, cloudy, gelatinous fluid, which clotted on standing, was withdrawn through a needle inserted into one of these areas, and as this was done the wall collapsed. A longitudinal incision was then made in the right dorsolateral portion of the cord through the entire extent of the tumor, and a large amount of degenerating tissue was removed. This was left open so that fluid, if formed, could pass directly into the cerebrospinal system.

Microscopic study of the tumor (fig. 3) revealed a well differentiated astrocytoma. Cells of both fibrillary and protoplasmic types were present.

Course.—The pain of which the patient complained before the operation was entirely relieved. His immediate postoperative condition was satisfactory, and convalescence was smooth, except for a heavy ache in each arm, which lasted only a few days. Neurologic examination at the time of discharge gave essentially the same results as before the operation. The wound healed by primary intention; the patient soon became able to walk, and required only an occasional mild hypnotic when dismissed from the hospital about three weeks after the operation.

In a communication two and a half months after the operation, the patient stated that although he had recently been confined to bed for ten days because of influenza, he had gained weight. His strength, however, was being regained slowly. He had not had the severe pain, numbness and prickling sensation, though he had had a constant dull ache in the right wrist and an occasional sharp pain that radiated into both shoulders. The incoordination of the right hand remained about the same, and the left hand was slightly involved. He required assistance in dressing, but was able to feed himself and to walk without aid. The spasticity of the right leg had also become less evident, so that he walked without a limp.

CARCINOMATOUS PACHYMENINGITIS

Report of a Case *

WALTER FREEMAN, M.D., PH.D., WASHINGTON, D. C.

This case is reported briefly because of the unusually widespread dural metastasis of a carcinoma of the prostate.

REPORT OF CASE

A white man, aged 53, was operated on for a carcinoma of the prostate on June 6, 1930. The wound healed slowly, and the patient complained of pain in the

Inner surface of dura showing widespread carcinomatous metastasis.

legs and back. The suspicion of metastasis was verified by roentgen examination of the pelvis and vertebrae, and later some pulmonary foci were observed. The course was progressively downward, but no neurologic symptoms were found.

Necropsy disclosed local recurrence of the malignant growth, with foci in the lungs and osseous system. When the scalp was reflected, wholesale invasion of the calvarium by malignant growth, especially on the left side, with irregular bosses about 5 mm. above the surface, was observed. Percussion of the skull yielded a soft, dull sound. The bone was easily cut and was somewhat thicker than usual. The inner surface was irregularly infiltrated by carcinoma, presented

* Submitted for publication, Aug. 3, 1931.

* From St. Elizabeth's Hospital.

a mottled appearance, and gave little sound when struck. The external surface of the dura was mottled in areas corresponding to those on the inner table of the skull, but it was not closely adherent. The inner surface of the dura was the seat of nodular excrescences, up to 6 mm. in diameter, filling practically every available space on the left side, and present to a somewhat less marked degree on the right (fig.). The nodules resembled the peritoneal metastases of ovarian growths. There was little adhesion to the underlying pia, and the falx seemed to have escaped involvement. The base of the skull and the dura covering it were free from nodules, and none were demonstrated in the substance of the brain. The brain was rather atrophic and had not suffered from compression.

News and Comment

AMERICAN NEUROLOGICAL ASSOCIATION

The Fifty-Eighth Annual Meeting of the American Neurological Association will be held in Atlantic City on June 6, 7 and 8, 1932.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The ninth annual meeting will be held at the Lord Baltimore Hotel in Baltimore, Feb. 18, 19 and 20, 1932. Dr. Ralph P. Truitt is chairman of arrangements.

Abstracts from Current Literature

LATE OCULAR MANIFESTATIONS IN EPIDEMIC ENCEPHALITIS. M. TEULIÈRES and J. BEAUVIEUX, Rev. d'oto-neuro-opht. **9**:349 (May) 1931.

In this report, made to the Fifth Congress of the French societies of oto-neuro-ophthalmology, both the sequelae and the new complications, manifested in the second phase of epidemic encephalitis, are described. In the initial stage, isolated ocular paralyses are found. These may disappear completely or, more rarely, may persist into the second stage. Disturbances of associated movements of the eyes are the rule in the second stage. The late ocular conditions may be classified as: (1) paralyses or deficiencies of the ocular musculature; (2) alterations of tonus or ocular bradykinesis; (3) the excitomotor syndrome.

Paralysis of convergence is almost always associated with external strabismus, troubles of accommodation or divergent strabismus. Sometimes convergence is preserved when the patient looks downward but is lost when looking upward or to the side. It may be associated with Parinaud's syndrome. Isolated paralyses are rare in the second stage of the disease, although they may occur. When they do, it is evidence of a lighting up of a latent focus of the infection. It is difficult to distinguish paralytic from labyrinthine nystagmus. The former appears with extreme movements of the globe and is a forerunner or a sequel of an alteration of associated movements. Inequality of the pupils represents a participation of the sympathetic or parasympathetic system. The Argyll Robertson pupil practically never exists in the second stage, but the loss of the reflex to accommodation is sometimes present. Perhaps there can be dissociation of the pupillary reaction and the function of near vision, but it is significant that the loss of pupillary reaction to accommodation with intact convergence has never been observed. Areflexia is very rare.

Ocular bradykinesis is manifested by: (*a*) fixed gaze; (*b*) the cogwheel phenomenon, and (*c*) pupillary and palpebral bradykinesis. All movements are initiated slowly and occur by jerks. Muscular hypertonia is often present. The fixed globes may suddenly be mobilized. Van Bogaert thought that the origin lay in the hypothalamostriate region, and Tinel and Baruk regarded it as the result of a mesencephalic angiospasm. The cogwheel phenomenon is dependent on muscular stiffness. "Spasms of torsion," especially of the cephalogyral muscles, may be present. The same phenomenon may be noted in the functions of the iris and palpebral muscles. Having closed the eyelids, the patient cannot open them for a time. On the other hand, there may be hypotonia, causing ptosis from muscular fatigability.

Ocular spasms may consist of spasmodic contractions in the state of repose or paroxysmic crises of function. Clonic blepharospasm exemplifies the former. The most characteristic of all the postencephalitic phenomena are tonic blepharospasm and oculogyral crises. In the former, the lids suddenly close for from a few seconds to several hours, after which the patient can open them. It is usually associated with other spasmodic manifestations. Oculogyral crises are merely a part of the general paroxysmic state. They may be tonic or both tonic and clonic. The most constant phenomenon is upward deviation. The crises occur suddenly and are beyond control; the relaxation is equally abrupt. Deviations in other directions are less common. Subjectively, there are pains in the eyes, a sensation of tearing of the muscles, photopsia, vertigo and diplopia. They are accompanied by jerking movements of the globes, fixed gaze, immobile facies, tonic blepharospasm, deviation of the head and neck, exaggeration of the parkinsonian manifestations, salivation, sweating, elevation of the hairs, pallor, clamminess and extreme anxiety. The duration of the spasm is variable. Of

the controlling influences, sleep is the most important. Repose, quiet, bandaging the eyes, the use of galvanic current and pressure over the ovarian region are helpful in preventing the crises. These crises may be aborted by exercise of the will, but it requires a tremendous effort. Various things may inaugurate a crisis, particularly physical or mental fatigue.

Since the study of ocular sensory manifestations by Valière-Vialeix, in 1925, the conviction is inescapable that they are caused by the encephalitic infection. They may occur as late manifestations of the acute stage or appear during the excitomotor phase. Among the first group are amaurosis without appreciable ocular lesions, retrobulbar neuritis, hyperemia and papillary stasis, retrochiasmatic lesions and lesions of the cortical visual sphere. Amaurosis is total or partial, appears suddenly and is transitory. Retrobulbar neuritis is usually bilateral, and, at first, there is no change in the optic disks or field changes may be present. It ends in primary optic atrophy which has no physical signs that differentiate it from other primary degenerations. The symptoms are varied, change from day to day and resemble those seen in cases due to multiple sclerosis. Signs of congestion of the nerve head are seen more often than other changes. Optic neuritis varies from a simple vascular dilatation to marked turgescence; it is often bilateral and varies in intensity and duration, and visual acuity is markedly affected. It may end in complete or relative recovery or in secondary atrophy. Papillary stasis is not so rare as was formerly thought. When it is a true stasis, it ends in complete recovery. Its characteristics are: rapid evolution, spontaneous regression and conservation of vision. Pseudostasis is accompanied by marked lowering of vision and modification of the fields, and ends in atrophy; it is really a neuritis, often confounded with choked disk. Exceptionally, retrochiasmatic and cortical lesions such as visual hallucinations, lateral hemianopia, photopsia, etc., have been reported.

Sensory ocular conditions appearing in the excitomotor stage are proofs of the persistence of the infection. A number of examples from the literature are recorded.

The discussion of the pathogenesis is illuminated by the schemas of nerve pathways of Dejerine and van Gehuchten. Functional associated ocular movements are induced by the will or reflexly; thus they are voluntary or automatic movements. For such synergized movements, association fibers between the nuclei, the supranuclear centers, or both, are necessary. Voluntary movements can be explained by the connections of the third and sixth nuclei with the cerebral motor cortex, but automatic movements, which are instituted by the occipital cortical zone, by impulses from the vestibular (eighth) and from the general sensory system (fifth), are more complex. "Besides their connections with the cortex (voluntary oculogyral and cephalogyral pathways) and with the reflex centers of the fifth and eighth nuclei (automaticoreflex oculogyral and cephalogyral pathways), the oculomotor nuclei are connected with each other and with the various bulbopontile motor nuclei by two association bundles, which borrow . . . the two oculomotor pathways; one ventral . . . the posterior longitudinal bundle, and the other dorsal, the posterior prelongitudinal bundle." The existence of supranuclear centers for coordinating associated movements is not proved. There is also a close connection of the corticonuclear and the pontinuclear pathways with the optostriate body, which presides over the postural and locomotor functions.

It is difficult to explain the late ocular paralyses and paralytic nystagmus in the light of present knowledge of the pathology. Various observers offer different hypotheses, and there is not a consensus as to the existence of supranuclear centers. Recent investigators tend to negative this hypothesis. Deficiencies of function in the second phase of epidemic encephalitis are seen especially in movements of elevation and convergence and less often in movements of laterality and depression of the globes. It is difficult to know whether these are due to tonic disturbances or to true paralysis.

The anatomic lesions are diffuse, but with a predilection for the gray matter of the mesencephalon; however, they are also found in the cerebral and cerebellar

cortex. The integrity of the oculomotor nuclei explains the absence clinically of dissociated paralysis. Alterations in dissociated movements of the eye may be the result of tonic modifications. Important factors in the production of hypertonia are alterations of the neuroglia of the subventricular region, the striopallidal system, the locus niger and the red nucleus, as well as degeneration of the sarcoplasm. In addition, reflex labyrinthine hypertonus, due to lesions of the vestibular system, is an important factor.

A number of theories in explanation of oculogyral crises are discussed, none of which is completely satisfactory. Weight must be given to the theory of vestibular disturbances, but it is evident that the matter is not so simple; the psychic factor also is imporant. Anatomists and experimenters think that the phenomenon is in close relation with lesions of the striolabyrinthine apparatus, certainly, also, with involvement of the mesencephalic vestibulo-ocular apparatus.

Amaurosis in the acute stage is explained by a vascular or perivascular inflammatory infiltration of the optic tract; retrobulbar neuritis, by an interstitial neuritis of the inferior optic pathway; papillitis, by an optic meningitis, and choked disk, by the presence of intracranial hypertension, although Tirelli thought it was due to direct compression from exudate. The lesions that cause the retrochiasmatic visual disorders are seated in the chiasm or the anterior end of the optic tract, the geniculate body and the hypothalamic region. In cases of transitory amblyopia and hemianopia, van Bogaert found lesions in the posterior optic radiations, and Valière-Valeix found similar lesions in cases with sensory visual disorders.

Lesions of acute epidemic encephalitis occur especially in the mesencephalon, the gray substance and the perivascular sheaths. They predominate in the cerebral peduncles, the locus niger, the third nuclei and the juxta-ependymal gray matter, but they may be much more widespread. Histologically, they consist of an interstitial infiltration, forming perivascular cuffs, and of disseminated inflammatory nodules, made up of lymphocytes and mononuclear neuroglia cells. In the second phase, the lesions consist of histopathologic modifications of the cerebrospinal axis, but these lesions alone do not sufficiently explain the complications. From an ophthalmologic point of view, there has been a dearth of necropsy observations in the parkinsonian period. The nodular formations persist. The work of Valière-Valeix, Anglade and van Bogaert showed the diffusion of the postencephalitic lesions and the almost constant participation of the corpus striatum, thalamus, the white substance of the optic radiations and the cortex of the rolandic and occipital zones. Anglade and Lasalle's study of preparations from the cerebral peduncle and inferior optic tract, from cases of postencephalitic bradykinesis, showed that lesions of the locus niger were the most constant. Only infrequently were slight lesions of the red nucleus noted. The third nuclei were markedly changed, owing to the fact that in all cases examined there had been paralysis of the third nerve. In the zone of the nuclear group were plaques of neuroglial sclerosis that enveloped and choked the nerve cells by their dense reticulum. These plaques were found also in the subependymal neuroglial stratum, the peduncle, the posterior longitudinal bundle and the quadrigeminate tubercles. The nerve elements were not entirely destroyed, which may explain their erratic and varied action. In sections of the optic nerve, chiasm, optic tracts and infundibulotuberian region, lesions predominated in the posterior part of the chiasm, along the tuberian region and near the geniculate body. They strongly resembled those of multiple sclerosis.

An extensive bibliography closes the article.

DENNIS, Colorado Springs, Colo.

THE POSTENCEPHALITIC MENTAL SYNDROMES. H. STECK, Schweiz. Arch. f. Neurol. u. Psychiat. **27**:137, 1931.

Since the figures are confusing and do not seem to tally well, it is difficult to summarize the statistical data presented in what is otherwise a valuable contribution to knowledge of the mental sequelae of epidemic encephalitis. Steck's

inquiry showed that 364 victims of encephalitis had been patients in Swiss asylums for mental disease and that only 14 of these patients had been free from mental symptoms. Parkinsonism was associated with mental disorder in 257 cases. Forty per cent of the patients in the group suffered from bradyphrenia alone or in combination with other psychic disturbances; the remaining 60 per cent showed character changes, as did 63 of a group of 81 patients not afflicted with parkinsonism (77.7 per cent). On the other hand, behavior disturbances were noted in only 20 per cent of 221 cases studied outside the state hospitals. The author has statistics to show that the two principal types of postencephalitic mental disturbance may coexist in the same case, and that either may be seen in persons of all ages, although bradyphrenia is more frequent in older and behavior disorders are more frequent in younger patients.

The author believes that the impertinence and lack of respect displayed by younger patients constitute the psychic counterpart of the hyperactivity and impulsiveness that characterize their general behavior. The hyperactivity and associated irritability is very likely to lead to an explosion whenever an attempt is made to restrain these patients. Their frequent importuning demands, their propensity for teasing as part of a general aggressive tendency, their wheedling obsequiousness combined with a characteristic "sticky attitude" ("attitude collante"), all of which may suddenly give way to the grossest impertinence, are commented on. The instincts, particularly the sexual and the food-seeking instincts, are often poorly restrained; exaggeration of the possessive instinct leads to the stealing of unnecessary articles. The behavior of the girls suffering from encephalitis often has an erotic coloring and they show a decided propensity for teasing, while boys, on the other hand, are often brutally aggresive. Previously suggested classifications for behavior disturbances were found unsatisfactory, since individual patients often presented symptoms characteristic of two or more of the proposed groups. In general, the prognosis of behavior disorders appears to be bad. Improvement was usually the result of restricted activity imposed by a developing parkinsonism; the essential traits of the altered character remained visible, however, behind the parkinsonian mask. Besides the "sticky affectivity" ("affectivité collante"), the author found the irritability, lability of humor, emotional incontinence and "versatility of affect" particularly tenacious. Lability and irritability were the most outstanding characteristics of the emotional disturbances displayed by adults who were suffering from parkinsonism.

In disagreement with Morsier, whose contribution appears in the same number of the *Schweizer Archiv für Neurologie und Psychiatrie*, the author believes that the postencephalitic behavior disturbances can be differentiated clinically from the endogenous psychoses. These behavior disturbances are essentially organic and resemble personality changes observed in epilepsy and in posttraumatic and postinfectious states. Steck has previously emphasized the "labilité massive" and the "affectivité collante" displayed by epileptic patients. Hereditary and constitutional factors seem to favor the development of character changes following encephalitis.

The severity of bradyphrenia was not found to be necessarily dependent on the severity of the associated parkinsonism. The author was able to demonstrate in cases of this sort a mental slowing that was sometimes irregular but always notable. A definite poverty of ideas (appauvrissement de la pensée) was indicated by the frequent stereotypy and the slight variation of the responses. In some cases, especially when the parkinsonism was severe, the slowing increased as the testing went on until a state of complete blocking was reached. In spite of the general apathy as evidenced by the narrowed fields of interest and a frequent indifference in regard to personal affairs, the patients with bradyphrenia generally maintained an affective contact with their families and other persons in their immediate entourage. A rather vapid and dull euphoria was observed now and then, but memory, judgment and orientation remained unimpaired.

The patients suffering from parkinsonism were more subject to fulminating depressive attacks of short duration than to depressions of the endogenous type.

The cases in which obsessions and compulsions occurred, though not very numerous, were striking. Phenomena of this sort were associated with respiratory disturbances and other tics in some cases. Oculogyric spasms were often, but not always, accompanied by anxiety states. In the few cases in which epilepsy has followed encephalitis, it has been, in the author's opinion, a matter either of coincidence or of the acute infection acting as a precipitant.

Some of the patients had hallucinations, and a few were paranoid at times, but, in addition, behavior disorders, obsessions, impulsions, oculogyric spasms or other evidence of a preexisting encephalitis were generally present in such cases. Even in cases in which symptoms were the most suggestive of schizophrenia, the "affectivité collante," the absence of true negativism and the conservation of the patient's personality all pointed to the true nature of the malady. These patients, furthermore, generally remained in contact with their environment and showed a more or less critical attitude toward their hallucinations. In a case of real schizophrenia, the symptoms were altered with the advent of parkinsonism to the extent that the clinical picture became more like that of a postencephalitic disorder. Steck believes that the association of schizophrenia with encephalitis may be largely a matter of coincidence.

In conclusion, the author expresses the belief that, in spite of their apparent variability, there is a certain unity in the psychiatric symptoms of the postencephalitic state, a unity assured by the very special coloring of the alterations in behavior. This coloring is based on a "special affectivity." The rarity of dementia in these cases and the close relation of the mental symptoms to the instinctive life of the patient indicate that the mental as well as the neurologic symptoms can be referred to lesions about the third ventricle and aqueduct.

DANIELS, Rochester, Minn.

INVESTIGATIONS ON THE PHYSIOLOGY AND PATHOPHYSIOLOGY OF COORDINATION. H. ALTENBURGER, Ztschr. f. d. ges. Neurol u. Psychiat. **129**:313, 1930.

Altenburger reports on two cases in which the afferent roots had been cut by Foerster, but in which the efferent roots were still intact. There is no unanimity of opinion about the state of affairs after section of the afferent roots. Foerster has pointed out that the completely deafferented arm can be moved immediately after root resection. In isolated movements of segments of the extremity the cortical impulses are delayed or even go astray, so that instead of flexion of the arm one may get extension. These disturbances are more marked in the distal segments of the arm, and are most pronounced in the fingers. The difficulty is so marked here that isolated movements of a finger or segments of a finger cannot be carried out.

In one case Foerster deafferented the arm, cutting the roots from the second cervical to the fourth dorsal. Cutaneous sensation was lost in the corresponding dermatomes; passive movements were not appreciated, and the stretch reflexes were completely abolished, as shown by the string galvanometer. Immediately after section of the posterior roots, movements could be carried out with the deafferented limb, but it was very ataxic. This stage was characterized by an overinnervation of the agonists so that the limb shot beyond its intended goal. Altenburger took action currents from the pars acromialis deltoidei before and after section of the root, and found that after section there was a great increase in the amplitude of the action current. This was still appreciable sixteen days after the section of the roots. Parallel with this increase in amplitude was an increase in frequency of the action current after section of the root.

The performance of voluntary movements after section of the dorsal root without the use of the eyes as a guide shows that rapid movements are done fairly precisely, but that slow movements are performed irregularly. In the rapid movements the loss of sensory control is noticed, after the termination of the movement particularly, by the presence of small, irregular movements. Coor-

dinated movement after deafferentiation is surprisingly good, at least as judged by the preceding case, but there is nevertheless a decreased conduction. The deafferented limb represented a markedly reduced movement mechanism in which a part of the effector organs were no longer present.

In a second case, Foerster cut the second lumbar to the third sacral roots. As in the previous case, immediately after the radicotomy there was an overinnervation of the agonists. This concept of Altenburger's has been criticized, and he therefore shows that action currents taken from the tibialis anticus twenty-four hours after radicotomy show an increase in amplitude and frequency as compared with the sound muscles. That this is not due to the synchronization of impulses that would ordinarily be out of phase is shown by the fact that simultaneous readings from different parts of the tibialis anticus give similar results. This increase in the amplitude of the action current persists during the weeks following radicotomy. The action current frequency is different for about fifty-seven days after section of the root (from 25 to 40 per second variation) but is much less marked after this. Dusser de Barenne obtained similar action currents after injections of procaine hydrochloride into the brachioradialis of a decerebrated animal.

After eight weeks, movements were carried out almost as precisely with the deafferented limbs as with the sound ones in both patients.

Altenburger states that his observations show that after section of all the posterior roots supplying a muscle, coordinated movements are possible to a surprising degree. From this it follows that the execution of a definite movement is carried out by the efferent roots without the help of the dorsal roots. Coordination is poor immediately after radiocotomy, but this stage disappears quickly, and is followed by good coordination, an adjustment that takes place spontaneously. Altenburger believes that the cortical centers come into play here; the cortex sends its impulses to the muscles concerned, and apparently displaces the afferent impulses of the dorsal roots.

Altenburger divides the phenomena that he observed into three stages: (1) incoordination is present immediately after radicotomy; (2) then there is relatively good coordination, in which the cortex comes into play; (3) loss of the afferent impulses is no longer recognizable, and movements are carried out with precision.

ALPERS, Philadelphia.

CONJUGATE DEVIATION OF THE HEAD AND EYES IN DISORDERS OF THE BRAIN STEM. L. J. J. MUSKENS, Monatschr. f. Psychiat. u. Neurol. **76**:268 (Aug.) 1930.

This article is a comprehensive review of anatomic, physiologic and clinical studies on conjugate deviation of the eyes and head. The author discusses the early clinical observations which indicated that this condition could be produced by a unilateral destructive lesion of fibers in the brain stem. These observations were confirmed by physiologic investigations. The results of experiments on the brain stem which the author regards as definitely established are stated as follows: 1. Electrical stimulation limited to the corpora quadrigemina does not lead to any movement of the eyes. 2. The nearer the point of stimulation comes to the posterior commissure, the more effect it has in producing conjugate deviation of the eyes. 3. Coordinated movements of the eyes do not occur following transection of the posterior commissure and the posterior longitudinal bundle. 4. It has not yet been proved that the posterior longitudinal bundle is receptive to direct stimulation between the nucleus abducens and the posterior commissure. 5. It has been shown that the pathway for voluntary conjugate movements of the eyes is not located in the pyramidal tracts. 6. Experiments in which the extrinsic muscles of the eyes were transplanted showed that the supranuclear systems concerned in conjugate movements of the eyes were very highly organized and capable of compensating for such changes. As regards experiments on the cerebral cortex, conjugate movements could be produced only by a strong stimulus. Hence

it is possible that they were due to extension of the stimulation to deeper structures, particularly the basal ganglia.

As a result of physiologic research, Muskens stated in an article published in 1902 that the posterior longitudinal bundle played an important rôle in the causation of conjugate deviation of the eyes in the horizontal plane. Hence his attention was directed to anatomic studies of this structure. It is strikingly similar in all vertebrates. The oral connections are as yet incompletely known. Some fibers end in the nucleus commissurae posterioris, the nucleus interstitialis and probably also the nucleus intracommissuralis. One bundle of fibers goes to the hypothalamus. There is still marked uncertainty concerning its relations with the thalamus. The vestibular connections consist in crossed and uncrossed fibers coming mainly from Deiters' nucleus. The ascending fibers give off numerous collateral branches to the nuclei of the nerves of the eye muscles. The author's previous work indicates that the posterior longitudinal bundle contains two descending groups of fibers. One extends from the nucleus of the posterior commissure to the medulla oblongata, and the other descends from the nucleus interstitialis to the sacral region. The theory has been advanced that the posterior longitudinal bundle is the pathway for a complicated reflex mechanism which has to do with automatic orientation in space and automatic adaptation to spatial relations. The observations of the author indicate that this is correct for orientation in the horizontal plane.

The clinical applications of the physiologic and anatomic studies of the posterior longitudinal bundle are discussed. Attention is called to the fact that conjugate deviation of the eyes to one side is identical with paralysis of gaze to the opposite side. Clinically, it is useful to differentiate chronic and acute forms of conjugate deviation. The former is almost always caused by slowly developing processes in the brain stem which interrupt the posterior longitudinal bundle between the abducens nucleus and the posterior commissure. The acute forms that disappear within a few days occur after cerebral injuries, particularly apoplectic lesions. In lesions of the brain stem there is ipsolateral paralysis of gaze, so that the conjugate deviation is to the normal side. However, a lesion of Deiters' nucleus or the medulla oblongata may lead to deviation ipsolateral with the lesion, owing to the fact that some ascending fibers from this nucleus cross to the opposite side. In deviation due to cerebral changes, the eyes are directed toward the side of the involved hemisphere. Some observers have noted that cerebral hemorrhages occasionally have an irritative rather than a paralytic effect, in which case there is contralateral deviation of the eyes. The common observation that in unilateral seizures the head and eyes are turned to the convulsed side cannot be used for purposes of cortical localization, for Muskens does not believe that definite proof has been offered that this phenomenon is a cortical one. He is inclined to attribute it provisionally to deeper structures, such as the corpus striatum or the globus pallidus.

ROTHSCHILD, Foxborough, Mass.

THE GENESIS OF HYDROMYELIA. GEORG SCHAETZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:1, 1930.

"Hydromyelia in relation to the spinal cord is in a certain sense the same as internal hydrocephalus is to the brain" (Kaufmann). In such cases the hydromyelia is nothing more nor less than a manifestation of a general dilatation of the cavities of the central nervous system.

Schaetz reports the case of an infant, of about 5 months, in whom meningitis developed, followed by an internal hydrocephalus. At necropsy the latter condition was found, together with a hydromyelia of the entire spinal cord. The entire ventricular system was tremendously dilated, and the foramen of Monro measured about 2.3 cm. The cerebellum was flattened out and pushed away by the markedly dilated fourth ventricle. The roof of the fourth ventricle was covered by a membrane composed of dura, arachnoid and a part of the choroid plexus. The cerebral convolutions were naturally much flattened out by the pressure. The

callosum was very small. The spinal cord when cut longitudinally looked like a sac, with a large cavity running its entire length. The walls of the cord measured from 1.5 to 2 mm. in the cervical region, 0.75 cm. in the dorsal region and from 1 to 1.5 cm. in the lumbar region. The sac was divided into numerous chambers by septums running here and there; these chambers were in communication with one another; their size varied a good deal, being largest in the cervical and lumbar regions, and smallest in the dorsal. Schaetz counted twenty-four septums in all, dividing the cord into chambers by their direction, running from side to side of the cord.

The case consists, therefore, of a high grade of hydrocephalus, with dilatation of all the cerebral cavities, as well as the foramina of Magendie and Luschka. The entire process was caused by an old meningitis that was most pronounced about the cisterna magna. In addition, however, there was an accompanying hydromyelia, which was separated from the hydrocephalus by a partially compressed but macroscopically intact portion of cervical cord. Microscopically, this portion of the cord was found to be penetrated by a dilated and compressed central canal. This separation of the hydrocephalus and hydromyelia by an intact portion of the cervical cord is of great importance.

Schaetz states that there is evidence pointing to the conclusion that spinal fluid is formed not only by the choroid plexus, but also by the ventricular ependyma and at the glial limiting membrane of the vessels. Dandy and Blackfan found an internal hydrocephalus developing, according to Schaetz, after plugging the aqueduct of Sylvius, despite the removal of both choroid plexuses. This seems to demonstrate that the ependymal cells of the ventricle can produce a spinal fluid in quantities too great to be absorbed readily. It will be recalled that the internal hydrocephalus and the hydromyelia cavities were separated by a short piece of compressed but otherwise normal cervical cord without hydromyelia, caused by compression of this part of the cord by the expanding cisterna magna, which insinuated itself down through the foramen magnum, and by compression of the upper cervical cord entirely obliterated the central canal and the subarachnoid space in this area. Schaetz believes that this is an exquisite natural experiment to demonstrate that the ependymal cells of the central canal of the spinal cord are capable of secreting spinal fluid. The hydromyelia could not have been an extension of the internal hydrocephalus, and must have been produced in this way. The case demonstrates also that the direction of flow of spinal fluid is from the periphery to the center, and that a dilatation of the central portion must result if the common outflow for brain and cord through the foramina of Magendie and Luschka is obstructed.

The formation of chambers in the spinal cord was probably formed in the areas in which the spinal nerves took their exit, forming an area of resistance to the fluid and producing a gliosis and the formation of septums in relation to the nerves.

ALPERS, Philadelphia.

A CONTRIBUTION TO THE STUDY OF THE NERVE ENDINGS IN THE SKIN OF THE HAND. R. MARTÍNEZ PÉREZ, Trav. du lab. d. recherches biol. de l'Univ. de Madrid **27**:187 (March) 1931.

Strips of skin removed shortly after death were fixed in a 10 to 15 per cent aqueous solution of chloral hydrate, and then hardened in absolute alcohol with a few drops of ammonia for twenty-four hours. The method of reduced silver nitrate of Cajal was used for impregnation. In order to study the distribution of Meissner corpuscles and the subbasal nerve plexus of the epidermis, sections were cut in most cases parallel to the surface of the epidermis. Skin from various regions of the hand was used.

Meissner corpuscles are most abundant in the palmar surface, especially in the distal portions of the fingers. The termination of the nerve fibers within the corpuscles takes place by means of neurofibrillar plates or disks, which are placed parallel to the surface of the skin. In this respect they resemble the terminations

of the corpuscles of Grandry. The nervous arborization is formed by one or two fibers wound more or less closely into a spiral. The fibers are of uneven thickness, and give off collaterals at various levels. The collaterals end in the plates or disks already mentioned. The numbers and complexity of Meissner corpuscles decrease in the dorsal surface of the hand. The absence of corpuscles coincides with the presence of hair follicles surrounded by large number of nerve endings. These "sensory" hairs seem to take the place of the Meissner corpuscles.

In the palmar surface of the hand, immediately under the epidermis and in contact with its basal layer, there is a plexus formed by nerve arborizations of extraordinary complexity. The arborizations are more elaborate in the finger tips. This is the subbasal plexus. The free nerve endings of the arborizations are placed between the ducts of the sweat glands, which in deep tangential sections of the epidermis appear arranged in rows lodged in the epidermal crests or elongated papillae. The arborizations are quite irregular; the finer twigs end in minute enlargements or in rather large, irregular bulbs in which the neurofibrils are clearly seen. In adults the twigs often end as rings. The relation of the terminations to the epithelial cells of the epidermis is clearly seen in vertical sections of the skin, particularly in young children. It is evident that many of the twigs enter the epithelium and end among the cells of the basal layer, or the layer above it, in relation with large, clear epithelial cells. These cells are homologous with the corresponding elements of the corpuscles of Merckel, which are so abundant in the pig snout. The actual endings appear as menisci closely applied against the surface of the epithelial cells just mentioned.

In addition to the subbasal plexus there is a superficial dermic plexus formed by thin bundles of fibers. The bundles anastomose to form a network of polygonal meshes. The center of each mesh is occupied by the duct of a sweat gland. From the bundles under consideration issue the fibers forming the arborizations of the subbasal plexus already mentioned. The complexity of this plexus and the fact that there is a definite relation between its arborizations and the sweat glands suggest that these arborizations may be concerned with a special type of tactile sensibility.

The deeper layers of the dermis of the dorsal surface of the hand have many sensory corpuscles, which are especially abundant in the phalanges. They are placed at various levels, and differ greatly in aspect. Most of these corpuscles are encapsulated, yet they differ markedly from the Meissner corpuscles not only in position but also in structure. Several types of corpuscles are described. Some of them are two or three times larger than the Meissner corpuscles; others are smaller. Some are formed by thin fibers arranged in a skein; others have thicker fibers with large, irregular varicosities. One or more fibers may enter into the formation of these corpuscles. The latter do not occur in the deeper layers of the dermis of the palm of the hand.

NONIDEZ, New York.

A FURTHER CONTRIBUTION TO THE THEORY OF FUNCTION OF THE FRONTAL LOBE. G. ENGERTH and HANS HOFF, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:332, 1930.

In a previous contribution it was shown that the origin of human gait from the quadruped position is due to the fact that the frontal lobe in its activity analyzes motor impulses from other centers. In this function the frontal and parietal lobes work together.

The first question that arises is as to the position of the center the function of which in quadrupeds is to mediate rhythm and the proper tonus in gait. It is known from the experiments of Wagner-Jauregg and Starling that dogs can still run with the pyramids cut. The pyramidal tracts cannot be the efferent aspect of the gait mechanism. Magnus has shown, moreover, that thalamus animals can also run, and that therefore the cerebral centers have nothing to do with the gait of the animal because the gait of animals without a cerebrum differs in no way from that of animals with the cerebrum intact. Engerth and Hoff

found that they could produce running attacks in an animal if they stimulated the transected brain stem in front of the anterior corpora quadrigemina. Stimulation of the brain stem at a level behind the anterior corpora quadrigemina caused no running movements. In the latter transection, the red nucleus is separated from the brain stem. The red nucleus is therefore necessary for normal gait rhythm. By a further investigation Engerth and Hoff were able to sever the rubrospinal tract in a dog. This dog was unable to walk, and running movements were likewise impossible. They conclude, therefore, that the functions of the red nucleus are: (1) the prevention of decerebrate rigidity and the distribution of normal tonus in standing; (2) action as a center for postural and standing reflexes; (3) action as the most primitive center for the walking act.

The red nucleus, therefore, acts as the deep center of quadruped gait. This is not to say that the other motor pathways have nothing to do with this act. Gait is modified and changed by the higher centers. Engerth and Hoff have shown that in man this fundamental rhythm of quadruped gait is changed by the activity of the frontal lobe. In this region of the cortex the tonus coming from lower centers is changed and passed on to other motor centers. The rubrospinal tract, which is important in lower animals, recedes in importance, and the pyramidal tract comes to the fore.

The question therefore arises whether with disturbance of the frontal region the fundamental gait rhythm will not come to the surface. The researches of Schilder have shown that loss of cortical centers makes manifest postural reflexes in man which are only rudimentary in the normal state. Engerth and Hoff had a number of patients with such lesions walk on all fours. They found that these persons reverted to a type of gait in which they put forth first left arm and leg and then right arm and leg, instead of left arm and right leg and vice versa. The question arises whether this gait rhythm is inherited or developed. Children learning to creep put forth first one foot and then the opposite hand. This occurs until the second year. Then this gait gives way to that already described for adults. The change in the gait runs more or less parallel with the speech development. Children who are backward in speech development creep by putting forth one hand and the opposite leg. It appears as if in man the development of the gait depends on a suppression of the deeper mechanism by the superficial, by a shunting of the walking mechanism from the deeper lying centers by way of the frontal lobe to the motor cerebral centers and the pyramidal tracts. Engerth and Hoff describe several cases of lesions of the frontal lobe in which there was a reversion to a primitive type.

ALPERS, Philadelphia.

MOVEMENT IN OPTIC IMAGES AND OPTIC IMAGINATION OF MOVEMENTS. LEO KANNER and PAUL SCHILDER, J. Nerv. & Ment. Dis. **72**:489 (Nov.) 1930.

The transformation of optic images has been described by Goethe, Purkinje, Johannes Müller and more recently by Urbantschitsch and Jaensch. The authors carried on their experiments with six adult physicians, four men and two women, all trained in self observation. Optic images wilfully produced showed fading, breaking of a line into fragments, diffusion of light, movements of a waving and curling character, scintillations, a tendency to multiplication, participation of the background and changes in the size of the object. With the duration of the imagination an increase in movement was observed. Marked individual difference in single subjects occurred, but many common trends were observed. Imagination of movements in animated objects was of absolutely natural character in some persons, while in others representation of natural movement was impossible despite serious effort. Movements were often jerky, with several sudden interruptions resulting in cessation of movement. In one observer the movement imagined was emancipated from the object and experienced as a violent shape. Changes in shape were general. A feeling of innervation within the imagining person was frequent, particularly in those who had difficulty in visualizing motion. Imagination of the

movements of the person's own body showed little difference from that of the movement of other persons, but kinesthetic sensations were usually stronger, as it is difficult to imagine one's own movements. The authors conclude that optic representation cannot be the basis for the performance of movement. Optic reproduction of previously perceived movements showed no continuity and often a vague shapeless something in movement with sometimes a transformation in the pathway. Aberration in the direction of movement was observed, while macroptic and microptic changes during the movement were common. The authors suppose that the final elaboration of the perception of a movement would take place under the interpretative influence of the entire situation in which the individual's own motion tendencies play an important part. A study of the individual difference of the observers is entered into, some showing jerky, bizarre or rhythmical motion, others natural motion, and one showing great difficulty in imagining movements at all. There was, however, hardly a reaction that could not be occasionally observed in every one of the persons examined. The hyperthyroid and the tetanoid types of imagination described by the Marburg school were also observed. A close analogy was seen with the observations in mescal intoxication, and Schilder has developed the thesis that what is going on in the fringes in a normal person becomes psychic foreground under unusual or pathologic conditions. Hence it is possible that agnosia brings to the fore experiences that normally remain in the background. Similar phenomena have been observed by von Weizsäcker, Hoff and Schilder in central and peripheral lesions of the vestibular nerve. Goldstein and Gelb have observed the influence on optic impressions of changes in tonus. Hence it is possible that there is a relation between vestibular and optic impressions of movement.

HART, Greenwich, Conn.

THE PROBLEM OF HALLUCINATIONS IN THE HEMIANOPIC VISUAL FIELD. A. HAUPTMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:90, 1930.

Studies of hallucinations in the hemianopic visual field began with Eskuchen (1911). He found practically always a disease of the cortex, with or without a simultaneous lesion of the optic radiations. He determined that involvement of the lateral occipital cortex was more apt to cause hallucinations than that of the mesial occipital region. He tried to differentiate between photopsias and hallucinations as a localizing phenomenon, indicating that the photopsias were due to cortical stimulation of the visual perceptive center, and hallucinations to cortical stimulation of the visual memory center. Henschen localized hallucinations as due to stimulation of the lateral occipital cortex. The calcarine area is not necessary for their production because they can occur after this is bilaterally destroyed. Horrax found that unformed hallucinations were due to involvement of the occipital lobe, and formed or complex hallucinations to involvement of the temporal lobe.

Schroeder opposed the view that hallucinations were an irritative symptom of a definite part of the nervous system. He pointed out the parallelism between hallucinations and dreams. Dreams, like hallucinations, are of a quantitatively decreased, but qualitatively unchanged, activity; they are not the expression of pathologically irritative events. One must, nevertheless, distinguish between simple and complex types of hallucinations. Stimulation of the occipital lobe causes primitive light phenomena which are encountered also in lesions of the optic nerve, retina, optic tract and radiation. Schroeder believed that the tendency to hallucinations in the blind visual field is due to the changed mental state of the patient. He ascribed it to an inability to differentiate between perception and projection. Schroeder, however, postulated that all the cases reported with hallucinations have been psychotic.

Hauptmann states that whenever there are visual hallucinations in the hemianopic field, there is an irritative stimulus somewhere along the optic system. This gives rise to photopsias which are changed to hallucinations. How does

this come about? There are several cases in the literature of a metamorphosis of this sort. Hauptmann believes that the visual hallucinations in the hemianopic field represent the subjective elaboration of a primitive visual sensation. The elaboration is dependent on the type of personality of the patient, on immediately preceding visual perceptions and on imagination. Cases are reported of hallucinations from the childhood scenes of a patient, of watch faces without hands in a watchmaker, of war scenes in a soldier, and of iron crosses in a wounded veteran. Kaplan reported hallucinations that concerned things of which the patient had thought immediately before. Other persons have hallucinated about the faces of men of whom they had been thinking. Sobol reported the case of a patient who hallucinated the form of the doctor who had just left. Uhthoff's patient, while in the hospital, hallucinated the form of a nurse.

ALPERS, Philadelphia.

HEPATIC DISEASE AND THE BRAIN; THE PATHOGENESIS OF WILSON'S DISEASE AND OF PSEUDOSCLEROSIS. EUGEN POLLAK, Jahrb. f. Psychiat. u. Neurol. **47**:195, 1930.

After an extensive review of the literature on the relationship between disease of the liver and that of the brain, Pollak describes in detail the case of a woman, aged 30, who suffered from severe hepatic disease for ten years and finally died in hepatic coma. During the last three months of life, a progressive parkinsonian syndrome developed. Necropsy revealed a secondary cirrhosis of the liver with severe endophlebitis of the hepatic vessels, obliteration of the portal and hepatic veins, with an extensive caput medusae. Gross examination of the brain showed only moderate depigmentation of the substantia nigra. The striatum showed no evidences of Wilson's disease. Histologic examination showed that: 1. Typical Alzheimer's glia cells were diffusely scattered throughout the entire central nervous system and were especially marked in the striatum, substantia nigra and dentate nuclei. In some areas, the striatum also showed accumulations of plasma cells. The second, third, fourth and fifth layers of the cerebellar cortex were relatively free from Alzheimer's glia cells, but the sixth layer as well as the molecular zone contained the greatest number of these cells. 2. The head of the caudate nucleus and putamen showed a "patchy" disease resembling that described by Spielmeyer in pseudosclerosis. 3. The striatum contained foci of edema and swelling. 4. There were very severe degenerative changes in the zona compacta, of the type usually observed in postencephalitic parkinsonism.

According to Pollak, this case may serve as an illustration that in hepatic disease of long duration the nervous symptoms do not appear until the terminal stage of the disease, and also that one need not have a liver typical of Wilson's disease to develop brain disease, but that any exogenous disease of the liver (a disease of the blood vessels with secondary hepatic degeneration) may produce the same result.

The case also raises some important questions as to the pathogenic relationship between the pathologic process in the liver and metabolism. The localization of the process in certain definite areas of the vascular network of the striatum is also noteworthy. Another striking feature is the disturbance of the water content in the brain. H. Mautner has shown that hypertonic solutions of dextrose exert a dehydrating effect on the liver. It is also known that similar substances produce cerebral edema. In other words, the action of hypertonic dextrose solutions is antagonistic in the sense that it decreases the water content of the liver and increases it in the brain. This naturally raises the question whether it is not a disturbance of the water metabolism in general that is the pathogenic factor in the production of the disease in the liver, which ultimately is followed by an increase of the water content in the brain with the final pathologic changes observed in this organ in the terminal stages of extensive disease of the liver.

KESCHNER, New York.

NYCTALOPIA. H. LAGRANGE, Ann. d'ocul. **167**:744 (Sept.) 1930.

Under the term "les petites hespéranopies" (slight hesperanopia), Lagrange classifies certain cases of mild night blindness. He practically adopts the terminology of Professor Frenkel, but reserves "petites hesperanopies" for those cases that are not explained by the usual symptomatology, in which no elevation of the threshold of luminous sensation is found and that some authors have rather carelessly named false night blindness because the condition was not demonstrable unless studied with unusual care. He points out that in former wars cases of night blindness were probably due in most instances to lack of essential food, and that during the World War the fatigue of trench life was probably more important than the avitaminosis. In studying the etiology of this condition, most authors have concluded that it is due to a high threshold for the sensation of light. There are, however, patients in whom the threshold for light is low and yet they are able to adapt normally; in spite of this they have nyctalopia. Lagrange believes that orientation in low illumination requires a physiologic mechanism that is not properly understood at the present time. The rôle of these factors appears even greater because the patients with nyctalopia frequently have trouble with orientation when the illumination is well above the threshold of sensation. The author alludes to the work of Roelofs and Zeemann, who show that the ability to judge distance and direction increases in direct proportion to the intensity of the illumination. He also refers to the work of Samelsohn, who has pointed out that differences in the light sense are practically always accompanied by alteration of the visual fields. Another important cause of poor night vision may be monocular amblyopia. The alterations in the size of the pupil undoubtedly play an important part in certain cases. Alterations in the crystalline lens also must play a part, and the author calls attention to the work of Hess on the influence of yellowing of the crystalline lens on vision. The latter studied the color perception in an eye with a yellow lens before and after the extraction of the cataract. The perception of blue was abolished by the yellow lens but was reestablished after extraction. In considering the neuropsychic factors Lagrange calls attention to the work of Truc, Kalt, Weekers, Magitot, Wessely, Tscherning and Danis. The consensus of these authors was that the cases of night blindness that they studied had a cause, and they favored as etiologic factors the causes outlined by Roelofs and Zeemann.

BERENS, New York.

FURTHER EXPERIMENTAL WORK ON BACTERIALLY-PRODUCED NERVOUS TISSUE LESIONS. DAVID ORR, Edinburgh J. Neurol. & Psychopath. **11**:97 (Oct.) 1930.

The histopathologic brain changes in seven rabbits into which bacteria had been injected intravenously are described. The brain in four cases showed necrotic areas, while a high degree of edema was present in the other three. No gross lesions similar to ischemic softenings, which characteristically are found in the cornu ammonis and the fornix, were present in the cerebral cortex, but coagulation necrosis was the outstanding characteristic change. The morbid change did not involve the entire depth of the gray matter, but included all the outer layers as far as the ganglionic lamina. In these outer zones the degenerated nerve cells were affected indiscriminately, ranging from a marked disturbance of many cells to the disturbance of but a few cells. The localities affected, the cortex, fornix and cornu ammonis, are all supplied by cortical vessels derived from the pia-arachnoid.

The most important portion of the paper is the splendid discussion of some facts concerning the cerebral circulation. There are two ultimate distributions of the cerebral vascular system, the vessels that subserve the gray and those that subserve the white matter. The evidence of this is seen in the histopathologic differences between cortical and subcortical lesions. The former are diffuse and consist of necrosis of the nerve cell units; the latter, as found in the fornix and cornu ammonis, involve a circumscribed locality and are typical of infarction. As the arterioles that supply the cortex and its adjacent subcortical zone have a common origin, the

pial arteries, the difference in type of the resultant lesions must depend on the anatomic arrangements of the fine capillary branches. The ischemic change found in a subcortical lesion can only be secondary to blockage of a terminal artery. On the other hand, the occurrence of coagulation necrosis of cortical nerve cells presupposes that the cortical arterioles are not terminal. The individual nerve cell units alone suffer and in a manner that points to an interference with their nutrition. This histologic picture is one that suggests, not ischemia, but rather a stasis caused by a narrowing of the richly looped arterial and capillary supply of the cortex.

The author attempts no explanation of the lack of coagulation necrosis in the multiform layer of the cerebral gray matter.

BECK, Buffalo.

LIGHT ALCOHOLIC INTOXICATION IN SCHIZOPHRENIA. A. A. PERELMAN, Rev. psychiat. neurol. & reflexol. (Leningrad) **5**:36, 1930.

The author decided to use alcohol in schizophrenia, basing the treatment on Pavlov's theory of schizophrenia as a state of inhibitions. Alcohol is known as a stimulating agent and also weakens the inhibitory centers in the central nervous system. It was decided to use alcohol in preference to ether on account of its continuous effect. The technic of the experiments was: Two or three hours before lunch the patients were given 25 cc. of a 50 per cent solution of absolute alcohol. If no results were obtained in fifteen minutes the dose was repeated. Another dose was given in fifteen minutes if no signs of intoxication appeared. The patients were observed during the intervals and for two hours after the alcohol was given. Twelve patients were tested in this manner. Inaccessible, stuporous patients were chosen for the experiment.

There was a great variability in a patient's willingness to drink the alcohol as well as in his susceptibility to it. Only in two cases did the alcohol not produce intoxication. There was a marked change in the psychomotor states of the patients. The faces became more expressive; some of the patients began to laugh or cry, and in most of them there was a marked vasomotor reaction. The movements became more alert and definite with a marked stimulation of motor areas. All patients took a great interest in their environment. They also became more communicative and accessible. Patients who had been mute for years became willing to talk, and their mental content became apparent. They expressed their ideas freely and acknowledged hallucinations that they had denied before. Psychologic factors and the various trends were brought to the surface during the intoxication. The moods varied from crying to euphoria or outbursts of anger.

A few hours after the intoxication the patients lapsed into the previous state. The author thinks that alcohol is a useful adjunct in the study of schizophrenia, because it stimulates the patients and also gives a good idea of what is going on in their inner lives.

KASANIN, Boston.

A CASE OF CHOROID PLEXUS PSAMMOMA IN THE RIGHT LATERAL VENTRICLE. A. TCHERNYSCHEFF, M. KOPYLOW and K. TERIAN, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:713, 1930.

The case reported was that of a child, aged 10, who since the age of 3 years had complained of headache and failing vision. Examination revealed bitemporal hemianopia, with bilateral choked disk and secondary optic atrophy, mild evidences of adiadokokinesia in both arms, dysmetria and intention tremor, hyperactive reflexes everywhere and a bilateral Babinski sign. Roentgen examination of the head revealed a dense shadow in the right lateral ventricle, conforming roughly to the shape of the latter. A diagnosis of hematoma or psammoma was made on the basis of the roentgenograms. Necropsy revealed a large tumor in the right lateral ventricle, extremely hard and grayish red. It was 9.1 cm. long by 3.8 cm. thick by 5.1 cm. wide. The tumor had crossed the midline through the right foramen intraventriculare and had penetrated into the left lateral ventricle. Here it compressed the thalamus, the stria terminalis and the nucleus caudatus. On the

right side it compressed the caudate and thalamus. There was marked hydrocephalus. Above, the tumor was adherent to the corpus callosum. It compressed the cortex, especially the occipital lobe. The tumor weighed 154 Gm., and histologically proved to be a psammoma.

Bruns showed that parasitic tumors are most common in the ventricles, and that true tumors are much rarer. Both forms are found chiefly in the fourth ventricle, less often in the third ventricle and least often of all in the lateral ventricles. True neoplasms of the ventricles are rare according to Bruns, and consist either of ependymal tumors or choroid plexus tumors. Cystic tumors, sarcomas and psammomas also occur. Davis and Cushing found only 6 tumors of the choroid plexus (papillomas) in 964 cases of brain tumor. McCarthy reported a cholesteatoma of the lateral ventricle, and Wätzold a perithelioma of the choroid plexus. Burmeister found a mixed tumor (chondrofibro-epithelioma) of the choroid plexus containing brain sand. Oberling found what he called a meningoblastoma in the choroid plexus, which was in part sarcomatous and in part angiomatous.

ALPERS, Philadelphia.

FIXATION OF ALCOHOL IN THE HUMAN CORTEX AND SUBCORTICAL GANGLIA IN ALCOHOLICS. P. E. DOBROVOTZKY, Medicobiological J. (Russian) **5**:117, 1929.

Studies were made of the brains of patients who had died from suicide, accident or asphyxia in a state of acute alcoholic intoxication. The autopsies were done three or four days after death. The alcohol content of the brain does not change for five or six days. Thus, the alcohol content of one hemisphere was the same as that of a corresponding area in the other hemisphere analyzed three days later. Reducing subsances other than alcohol are present in the brain, but the amount is extremely small when compared with the alcohol content. The alcohol content was determined by Rappoport's method as modified by the author; it is based on the principle that alcohol in the presence of sulphuric acid and potassium permanganate is reduced to an acetyl aldehyde.

Seventy brains were studied. In sixty cases only one hemisphere was analyzed; in the other ten both hemispheres were studied. Thin slices of gray matter were removed from the following areas: (1) the area gigantopyramidalis, (2) the regio postcentralis, (3) the regio supratemporalis, (4) the regio frontalis, (5) the area striata, (6) cerebellum, (7) the vermis, (8) the striatum, (9) the pallidum and (10) the ganglion stellatum. In a control group of persons who had not taken any alcohol, the gray matter showed only the faintest traces of reducing substances; they could not even be estimated quantitatively. On the other hand, in the brains of alcoholic subjects the various areas in the brain showed definite amounts of reducing substances, the minimum being 0.22 mg. per hundred grams of brain substance; this is from 100 to 200 times as much as the amount found in the brains of nonalcoholic persons. The richest alcohol content was found in the cerebellum; it ranged around 10 mg. per hundred grams; the smallest amount was found in the basal ganglia. It is well known that the clinical manifestations in alcoholism are cerebellar (loss of equilibrium) and vegetative (breathing, pulse, etc.). It is interesting to note that these areas contained the richest amount of alcohol.

KASANIN, Boston.

THE PHYSICOCHEMICAL CHANGES IN PREGNANCY IN THEIR RELATION TO NEURAL AND MENTAL DISTURBANCES DURING THE GESTATION PERIOD. L. SEITZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:348, 1930.

Seitz has found definite evidences of physicochemical changes in the body of the pregnant woman. Chief among these are the changes due to activity of three glands: the pituitary, ovary and thyroid. That there is a definite sex-producing hormone in the first of these has now been shown by the work of Ascheim and Zondek. Furthermore, quantitative studies have shown that there is an increase

in thyroxin in the body during pregnancy. In the blood there is a decrease in albumin and an increase in the quantity of water. The globulin and fibrinogen components are particularly increased in the albumin bodies. In contrast to the albumin, the fat content of the blood is definitely increased. This includes neutral fat as well as lipoids. Of the latter, lecithin and cholesterin are increased in equal amounts. Other lipoids must also be increased, but there is no definite evidence of this.

The sedimentation of red corpuscles is increased as pregnancy advances, and there is a shift of the leukocytes to the left. Thrombocytes are increased in the blood stream, and this, together with the increased fibrinogen, explains the tendency to thromboses in pregnancy. The calcium content of the blood is somewhat diminished toward the end of pregnancy. It was formerly believed that there was a slight shift to the acid side in pregnancy, but studies from Seitz' clinic show that the normal alkalinity of the blood is usually maintained, and that a shift to the acid side rarely occurs.

The irritability of the muscles is increased in about 80 per cent of pregnant women. Electrical stimulation shows that it is necessary to use only 50 per cent of the strength of cathodal closure current in order to cause contraction. The vasomotor system reacts more irritably. Dermographia is often seen, and the tendency to urticarias, erythemas and other vasomotor disturbances is well known.

ALPERS, Philadelphia.

CHANGES IN THE NERVE FIBERS IN MULTIPLE SCLEROSIS. L. JABUREK, Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **33**:93 (Feb.) 1931.

The changes in the nerve fibers in multiple sclerosis were studied by Jaburek in six chronic cases of this disease. He found that in every case the changes in the fibers began either with a circumscribed or with a diffuse swelling. The myelin sheaths disintegrate sooner than the axis cylinders. Slight degrees of swelling leave no microscopic residua, whereas more severe swellings — those in which the neurofibrillae are destroyed transversely — lead to secondary degeneration. The great variations in the sclerotic foci depend preeminently on the variations in intensity of the primary swelling of the nerve fibers. The acute axonal changes, characterized by irregular swelling with loop formation, unequal impregnability, fragmentation and granular disintegration, as well as whorl formation, seem to go hand in hand with the acute stage of swelling, provided that the latter is sufficiently severe to lead to dissolution of the substance of the axons, especially of the neurofibrillae. In less severe swellings of the nerve fibers these acute manifestations of axon disintegration are not observed, and by the time the swelling has completely subsided restitution is fully established. Almost simultaneously with the acute destruction of the axis cylinders there occurs regeneration of the neurofibrillae. The changes in the myelin sheaths are less marked. As soon as the swelling passes beyond a certain point there occurs an apparently irreparable degeneration of the myelin tube. The entire process of destruction of the myelin sheath is much slower than the process of degeneration and repair of the axis cylinders. While the axis cylinders show the most marked alterations the sudan reaction is still negative, but when this reaction is positive, in the very earliest stages of the sclerotic process, and when well formed myelin ball rests can still be found, those axons that have not as yet undergone secondary degeneration begin to reveal evidences of restitution and show no further changes during the later development of the sclerotic scar.

KESCHNER, New York.

THE SYMPATHETIC INNERVATION OF THE STOMACH: II. THE EFFECT OF STIMULATION OF THE PERI-ARTERIAL NERVES ON THE STOMACH AND SMALL INTESTINE. B. A. MCSWINEY and J. M. ROBSON, J. Physiol. **71**: 194 (Feb.) 1931.

This paper deals with the effects of stimulation of the vagus and periarterial nerves supplying smooth muscle preparations, and affords further evidence to

demonstrate that motor and inhibitor effects may be obtained from the smooth muscle of the stomach on stimulation of sympathetic nerves. Rabbits and cats were used. The stomach was removed from the animal; the coronary artery was identified and dissected free from the surrounding tissue. The division supplying the body of the stomach was separated from the main artery, and the strip of muscle supplied removed free from mucous membrane. A strip of fundic muscle supplied by the main artery was also obtained. Preparations of small intestine with the mesenteric arteries were also made. The technic and records obtained are explained.

The reaction of the gastric muscle depended on the type of stimulation employed. Stimulation of the nerves with frequencies of from 1 to 12 break induction shocks per second caused contraction of the muscle; with 20 to 50 shocks per second, relaxation was obtained. Reversal effects were also recorded by varying either the strength of the current or the duration of the faradic stimulation. The motor response was abolished by the addition of ergotoxine or atropine. The movements of the intestine were inhibited by all types of stimulation. The latent periods of contraction and relaxation were recorded and compared with the latent periods obtained on stimulation of the vagus nerve. Evidence is put forth to show that the motor and inhibitor responses are due to stimulation of sympathetic fibers conveyed in the periarterial nervous network.

ALPERS, Philadelphia.

AGNOSIA OF THE FINGERS AND AGRAPHIA. (A PSYCHOPATHOLOGIC STUDY.) J. LANGE, Monatschr. f. Psychiat. u. Neurol. **76**:129 (July) 1930.

The condition described by Gerstmann as agnosia of the fingers is a definite syndrome that is by no means exceptionally rare. It is characterized by inability to distinguish the fingers from one another, slight agraphia, impairment of orientation for right and left and inability to use figures, particularly in attempting mathematical calculations. Occasionally there is a loss of optokinetic nystagmus. Lange reports the results of an exhaustive investigation of a patient showing this syndrome. The patient was unable to distinguish right from left, above from below and front from behind. Only the simplest calculations could be performed. Larger numbers, which introduced a spatial element, could not be manipulated correctly. Writing, drawing, arranging letters on blocks into the alphabet and similar performances were defective. Lange comes to the conclusion that the fundamental disturbance was a loss of the more abstract conceptions of direction in space. He compares his case with the cases of amnesic aphasia described by Goldstein and Gelb. In the latter there was a general impairment of abstract thought, hence a sinking to a lower mental level, whereas in the former only a particular type of activity suffered. This is due to the fact that in the case described in this article the lesion was situated in the so-called periphery of the cerebral cortex. However, the author doubts whether a strictly circumscribed focus ever leads to a general lowering of the mental level. A second case is reported in which postmortem observations confirmed the view of Herrmann and Pötzl that the syndrome of agnosia of the fingers is produced by a lesion in the region between the left angular gyrus and the second occipital convolution.

ROTHSCHILD, Foxborough, Mass.

THE PRACTICAL AND THEORETICAL SIGNIFICANCE OF THE PROTEIN DETERMINATIONS IN THE CEREBROSPINAL FLUID IN NEUROLOGIC CASES. H. DEMME, Arch. f. Psychiat. **92**:485, 1930.

The results of the determination of proteins by the Kafka method in 2,000 cases are reported. This method consists in first determining the amount of total proteins by the use of the Esbach reagent; only 0.6 cc. is used in this determination. The amount of globulin is determined first with the ammonium sulphate method, and then also with the Esbach solution. This is subtracted from the total protein,

thus obtaining the amount of albumin. The so-called protein quotient is then determined by dividing the amount of globulin by that of albumin.

The cases studied represented different types of nervous and mental diseases, and Demme found significant deviations from the normal in a surprisingly high percentage. Some of the conclusions are as follows: 1. The method described is the most useful for practical purposes, because it is easy to perform and requires very small quantities of fluid. 2. The determination of the protein and the relationship between its different components, as well as with the other contents of the spinal fluid, is of great importance diagnostically. The following are only a few of its uses: It can be used in the differentiation of acute infections of the central nervous system, in the differentiation of meningitis from sympathetic meningitis, in the differential diagnosis of syphilitic disease of the central nervous system and in the evaluation of sequelae to injuries to the skull. 3. In a number of diseases in which other methods do not show any deviation from the normal, definite changes were found by this method (Parkinson's disease, chorea and others). 4. The method permits further insight into the nature of the cerebrospinal fluid.

MALAMUD, Iowa City.

HISTOPATHOLOGY OF EXPERIMENTAL DIABETES INSIPIDUS. FRANCIS J. WARNER, J. Nerv. & Ment. Dis. **73**:375 (April) 1931.

Polyuria due to puncture of the hypothalamus has been studied by Camus, Roussy, Bailey, Bremer, Curtis and others, but the histopathology of the lesions as well as their anatomic localization in the hypothalamus has not been studied. Two dogs are described in which after complete hypophysectomy by the transpalatosphenoidal route polyuria developed. The lesion in one dog was situated in the anterior part of the hypothalamus, the lowest and largest lesion being situated in the area of the preoptic and anterior hypothalamic nuclei, the filiform nucleus and dorsal tip of the dorsomedial hypothalamic nucleus. The lesion in the second dog was situated in the hypothalamus just anterior to the infundibular stalk, involving the nucleus tuberis. Enormous proliferation of microglia, with gitter cells and macrophages, were found microscopically in these spots. Proliferation of new vessels and degeneration of ganglion cells were noted. In both dogs there was no marked metabolic disturbance in spite of complete extirpation of the hypophysis. The experiment indicates the presence of centers in the hypothalamus that may control the urinary output by regulating the metabolism of water and also that it is the injury to the hypothalamus rather than the hypophysectomy that causes the permanent polyuria. The latter conclusion the author draws from the fact that in only one of the animals was the hypothalamus injured at the time of the hypophysectomy, and this was the only one to develop permanent polyuria. The first hypophysectomized animal, in spite of four hypothalamic punctures, did not develop permanent polyuria. These observations agree with Leschke, Camus and Roussy who, however, did not make accurate neurologic studies of the brains of their animals.

HART, Greenwich, Conn.

NEW CONTRIBUTIONS TO THE HISTOPATHOLOGY OF LECITHINOID DEGENERATION. T. VON LEHOCZKY, Arch. f. Psychiat. **92**:591, 1930.

The problem of lecithinoid degeneration is discussed on the basis of a study of twenty-two cases, including three cases of jaundice, two of diabetes, five of alcoholism with cirrhosis, one of eclampsia, one of a puerperal psychosis, one of carcinoma, one of hyperthyroidism, and eight of uremia. He found lecithinoid substances in fifteen of the cases, mostly in those in which there was disease of the liver. The lecithinoid substance, which is much like that found in the nerve cells in Tay-Sachs' disease, was found in the nerve cells, glia and vessel walls. In some cases, the substance could also be demonstrated in the liver. In the brain, it was found especially in the cornu ammonis, to a certain extent in the striate body and also on the inferior surface of the frontal convolutions.

Lehoczky was of the opinion that this substance actually develops in the cell elements as a product of degeneration. This is due to the invasion of the brain by toxins released by certain types of diseases (especially those of the liver), which cause a series of changes, one of which is this type of degeneration. In certain parts of the brain, where the circulation is not as efficient as in others, the products after their development remain in the cells. In contradistinction to Tay-Sachs' disease, lecithinoid degeneration affects not only the ectodermal tissues but also the other elements. Furthermore, in these cases the substance shows a predilection for certain localities. These differences are probably dependent on the fact that this disease is exogenous.

MALAMUD, Iowa City.

ORGAN JARGON. F. G. CROOKSHANK, Brit. J. M. Psychol. **10**:295 (Jan.) 1931.

The author points out the need for greater correlation between mental and physical states and the recognition of better balanced generalizations regarding the responses of the organs to emotional traumas. He compares those who treat such organ responses directly to the housemaid who takes the receiver off the telephone in order to keep it from ringing. He quotes Creighton, who in 1886 described neurotics as "persons whose unconscious memory for unconscious reflex effects is particularly strong," and concludes that when feelings are blocked or unexpressed they may be expressed in visceral reactions. This is one theory of organ jargon. He then reviews in a favorable note Adler's view of correlation between emotional tension and visceral symptoms. Migraine is regarded as an expression of rage that has had no other mode of expression. He reviews other visceral disturbances that have a close relation to emotional explosions, and shows how the organ response is a substitute for the emotional one. He sees the divorce of academic medicine from psychologic medicine as growing out of the establishment of autonomous specialties in medicine, which has been "the prelude to the decay and fall of medicine as a coherent discipline," and offers a great opportunity for the quack, the "boastful pretender to medical knowledge." The inroads of the quack can be prevented only by bringing about better understanding of integration and "the unity of the individual in health."

ALLEN, Philadelphia.

PARADOXICAL EMBOLISM OF THE BASILAR ARTERY. STANLEY J. HARTFALL, Lancet **1**:700 (March 28) 1931.

A case of paradoxical embolism of the basilar artery is described. The patient, a man, aged 49, had had a compound fracture of the right tibia and fibula, with severe laceration of the leg. Thirty-two days after the injury, after having made satisfactory progress, he complained of numbness of the leg and tightness in the chest. He suddenly lapsed into unconsciousness, demonstrating noisy Cheyne-Stokes respiration. There were generalized convulsive movements and a tendency to opisthotonos, while general spasticity with increased tendon reflexes and bilateral Babinski responses rapidly developed. The eyes showed occasional, irregular, jerking movements to the right. The left pupil was small and fixed, the right dilated and also nonreacting. The heart appeared normal, but there was evidence of right pulmonary embolism. Death occurred in eight hours. Embolism of the pulmonary arteries was found at autopsy. A large patent foramen ovale and paradoxical emboli in the basilar artery were present.

The diagnosis of paradoxical cerebral embolism was made on the following grounds: the sudden cerebral accident, the presence of signs in the chest compatible with infarction of the lungs, the absence of signs of cardiovalvular disease, and the presence of a wound with the past history of sepsis. Thus was introduced the possibility of venous thrombosis. The main interests in this case are, first, the signs of basilar artery embolism, which is in itself a rare condition and one infrequently observable, and, second, the possibility of a paradoxical embolism occurring in the cerebral vessels due to a patent foramen ovale.

BECK, Buffalo.

AN INVESTIGATION OF THE NERVOUS SYSTEM AS A POSSIBLE FACTOR IN THE REGULATION OF CILIARY ACTIVITY OF THE LAMELLIBRANCH GILL. ALFRED M. LUCAS, J. Morphol. & Physiol. **51**:147 (March 5) 1931.

In the lamellibranch gill, variations in ciliary activity occur that are due to causes other than changes in the external medium, and these variations occur as readily in gill filaments detached from an animal as they do in those that are attached. Electrical stimulation of the branchial nerve or the cerebrovisceral connective nerve causes a slight muscular movement of the gills, but has no effect on the ciliary activity of the frontal, the laterofrontal or the lateral cilia. It seems probable that nerves do not enter the gill filaments, even though in Mytilus and Modiolus, contractile cells are present as well as gland cells and ciliated epithelium. The laterofrontal epithelium is not a syncytium, the cells that compose it being bounded on all sides by cell walls. The ciliary rootlets of the laterofrontal and lateral cells terminate in the cytoplasm of the nuclear zone. From a study of wavelength, rate of wave propagation and frequency of vibration of laterofrontal and lateral cilia, it is suggested that the coordination impulse passes through the cytoplasm of the cell, and that the system of diverging rootlets in the laterofrontal cells serves the purposes of carrying the impulse simultaneously to all cilia within a single cell. The fact that the inhibition impulse travels more rapidly than the coordination impulse indicates that they have different pathways. The nerve cells of the visceral ganglion form osmiophilic granules; connective tissue cells are present in the nervous system, and the nerve fibers are surrounded by clear liquid spheres the surface tension of which is lowered by the addition of alcohol.

WYMAN, BOSTON.

THE OCULAR FORM OF SEROUS CIRCUMSCRIBED BASILAR MENINGITIS. D. MICHAIL, Ann. d'ocul. **167**:642 (Aug.) 1930.

Michail points out that the study of circumscribed serous meningitis dates from the work of Emerson and Frazier in 1906. These authors in operating on tumors of the cerebellopontile angle found serous cysts. Michail stated that recently he had an opportunity to study a case of meningitis of the circumscribed serous basilar type with manifestations that were purely ocular. He gives the following summary of the case:

A woman, aged 22, complained of headache accompanied by disturbances of vision and diplopia caused by paresis of both sixth nerves. The condition was improved by lumbar puncture, but seven months later the patient again complained of severe headache accompanied by slight fever and serious impairment of vision of the right eye, caused by optic neuritis with marked edema. These symptoms were alleviated by lumbar puncture and intravenous injections of mercuric cyanide. Examination of the spinal fluid during these attacks showed normal tension, a negative Wassermann reaction and a mild lymphocytosis of 7.5 cells per cubic millimeter. Roentgenograms revealed an opacity at the base of the skull and slight narrowing of the optic canal on the side of the optic neuritis.

Michail considers that the case is one of circumscribed serous meningitis, subacute in character, with a remission of one year. He thinks that in this case the meningitis was due to a mild nasopharyngeal infection. He was unable to find reference to a similar case in the literature.

BERENS, New York.

PYREXIAL TREATMENT OF THE G. P. I. WITH SULFOSIN. J. H. R. LAPTAIN, Lancet **1**:635 (March 21) 1931.

Twelve patients with dementia paralytica were treated with sulphur in olive oil (Leo). The average temperature in an individual course was 103.2 F., and in the entire series but one rigor occurred. The maximum dose required at one injection seems to be 10 cc. An increased dosage has neither elevated the temperature appreciably nor brought on the reaction more quickly. The time of temperature elevation seemed to show a marked constancy between nine and

twelve hours. All cases were in an advanced stage of the disease. Eight patients were intractable, maniacal and vividly hallucinated. A course consisted of from five to seven injections, followed by one month's interval. The mental improvement became apparent after a few injections. The physical changes noted were an increase in weight and a reduction in anemia. Of the twelve patients, two were discharged recovered and two were well enough to be placed on a trial period. All the rest, with but one exception, have shown amelioration of the symptoms in varying degrees, the exception being an advanced case in a patient who is unlikely to recover.

It was concluded that treatment with sulphur in olive oil is eminently suitable in advanced cases because of its harmless effects, particularly on a degenerated myocardium. The facility of regulating the temperatures and of procuring the material widens the scope of the treatment, while the results obtained compare favorably with statistics of induced malarial pyrexia.

BECK, Buffalo.

DEMENTIA PARALYTICA AND SYMMETRICAL GANGRENE. V. CHALLIOL, Arch. gen. di neurol. e psichiat. **11**:341, 1930.

The author reports a case presenting clinical and serologic signs of dementia paralytica. After an exposure to cold the patient developed acrocyanosis which was followed by gangrene of the hands and feet on both sides. There was found a neurovegetative imbalance in the sense of sympathicotonia. The patient had no diabetes; no febrile infectious diseases had preceded the development of the Raynaud's syndrome; there was no history of ergot or carbon monoxide poisoning. It was more difficult to exclude Buerger's disease; however, on the grounds of the acute development of the symmetrical acrocyanosis following exposure, the absence of vasomotor reaction in the affected parts in relationship to the position of the extremities, which are pathognomonic of Buerger's disease, the author declines to accept the hypothesis of thromboangiitis obliterans. The patient was submitted to mercurial antisyphilitic treatment (0.05 Gm. mild mercurous chloride intramuscularly every four days). After three injections the spread of the angioneurotic process was arrested. After eight injections a good line of demarcation was formed between the zone of the asphyxiated and the normal tissue; the granulation tissue gradually acquired a better appearance; the seropurulent secretion diminished and eventually disappeared. The author regards this case as a rare example of dementia paralytica associated with angioneurotic gangrene, caused by exposure and favored by a syphilitic endarteritis and by a neurovegetative imbalance.

YAKOVLEV, Palmer, Mass.

SIMULTANEOUS REGISTRATION OF THE INTRA-OCULAR AND CEREBROSPINAL FLUID PRESSURES. E. MARX, Ann. d'ocul. **167**:1001 (Dec.) 1930.

It is pointed out by Marx that uncertainty still exists in regard to the question of the intra-ocular pressure, under both normal and pathologic conditions. His researches were first made on rabbits and on cats because they withstood ether better. The intra-ocular pressure and the pressure in the cisterna magna were studied simultaneously. He obtained the following results: 1. The injection of a solution of sodium chloride, isotonic with the blood, into the venous system produced no change or only a slight increase in pressure in the eyeball and in the cerebrospinal fluid. 2. Hypertonic solutions of salt caused a lowering of pressure in the two systems. 3. Hypotonic solutions produced an augmentation of the pressure in the two systems. 4. The change in the pressure was always simultaneous, although rarely equally pronounced in the two systems. The intensity in the change of pressure is independent of the absolute pressure in each of the systems. 5. He was never able to determine a change in the pressure in the two systems in which the pressure became elevated in one and lowered in the other.

He concludes that the parallelism between the pressure in the eye and the pressure in the cerebrospinal fluid is established by these researches, and that

one may possibly conclude, that, in the eye, there is also a more or less complete parallelism between the intra-ocular and the cerebrospinal venous pressure. The possibility that this relation existed has been previously mentioned by Bailliart and Magitot.

BERENS, New York.

THE INITIAL AND RECOVERY HEAT PRODUCTION OF VERTEBRATE NERVE. D. W. BRONK, J. Physiol. **71**:136 (Feb.) 1931.

The experiments reported in this paper constitute a redetermination of the course of the heat production accompanying activity and recovery therefrom in vertebrate nerve. The two important instrumental improvements used were a new type of thermopile and an improved moving magnet galvanometer. Six or eight pairs of sciatic nerves from three or four large Hungarian frogs were used for each experiment. The technic is given in detail.

Many of the essential observations of earlier workers have been in large part confirmed. An analysis of the course of the heat production resulting from a stimulus lasting from nine to fifteen seconds shows a progressive increase in the rate of production of heat during the period of stimulation. This is the sum of the heat associated with the conduction process and that accompanying the recovery therefrom. The production of heat during recovery is at a maximum rate immediately following the end of stimulation and continues for some minutes at a decreasing rate. The duration of this recovery phase is largely dependent on the temperature. At 19 C., it was about eleven minutes, and at from 24 to 25 C. about seven and three-fourths minutes.

From seven experiments, comprising about seventy individual determinations, the initial heat production has been found to be 8.9 per cent of the total. This is compared with the earlier determination of 11 per cent for frog's nerve and Hill's recent value of 2.25 per cent for crustacean nerve.

ALPERS, Philadelphia.

THE SIGNIFICANCE OF LOMBROSO FOR MODERN BIOLOGIC CRIMINOLOGY. F. VON ROHDEN, Arch. f. Psychiat. **92**:140, 1930.

In modern investigations of the development and nature of the criminal there has been a tendency away from the thoughts expressed by Lombroso. This has probably been caused by the somewhat extreme interpretations that were added to the central features of the theory by Lombroso himself, and especially by some of his followers. Von Rohden takes the stand that modern investigations of body type and constitution show definitely that one of the central features of Lombroso's theory is supported by facts. He sees two important components in the theory. The first is that there are born criminals. The second deals with certain morphologic signs that characterize such persons. It is the second feature in Lombroso's theory that served to discredit even the truth that is contained in the first. No single physical mark of degeneration, or for that matter any number of such marks, could brand a person as a criminal. They may suggest the possibility of an atavistic tendency, but do not necessarily condemn him to a criminal career. On the other hand, there is no question but that certain persons are born with psychopathic predispositions who, when given a certain type of environment, will develop into criminals. This component, then, of the theory of Lombroso that states that constitutional predispositions toward a criminal career are actually found in a certain percentage of criminals is just as true today as it was when Lombroso first formulated the theory.

MALAMUD, Iowa City, Iowa.

TUBERCULOSIS AND DEMENTIA PRAECOX. H. CLAUDE and BARUK, Paris méd. **2**:571 (Dec. 27) 1930.

Ten cases are described in which an evolving tuberculosis that became torpid, a torpid tuberculosis that grew worse, and an evolving tuberculosis with remissions constitute the three forms under consideration. The mental disturbances accompany

chiefly the torpid phase and disappear or become milder in the evolving phase. The toxic factors play a leading rôle, increasing the complicated, often contradictory psychomotor automatism, which, according to the author, is a peculiar psychic state between sleep and coma, characterized by restlessness and sleeplessness, and which one might term cataleptic sleep. This seems to rest on a toxic infection of medium grade. One can thus speak of a syphilitic as well as a tuberculous catatonia. Today, catatonia is too often regarded as a local disease, in spite of the toxic intestinal disturbances, disorder of the general metabolism and arthritic manifestations. Certain confusional states and many psychic disturbances and character alterations, which are often found in tuberculous patients, may be explained on the basis of meningitis. In one case such disturbances were due to a pleural infection. It appears also that many tuberculous patients present a general toxic disease which is first detected in functional disturbance of the nervous system. On this basis many cases of schizophrenia can be explained in which the hereditary anlage is to be considered as well.

HART, Greenwich, Conn.

INVESTIGATION OF THE ALKALI RESERVE OF THE BLOOD AND URINARY HYDROGEN ION CONCENTRATION IN EPILEPTIC PERSONS DURING AND BETWEEN CONVULSIVE SEIZURES. F. DI RENZO, Riv. di pat. nerv. **36**:549 (Nov.-Dec.) 1930.

The conclusions reached by Dr. Renzo are:

1. That convulsive seizures are preceded by an increase in the alkali reserve of the blood which is manifest from twenty-four to forty-six hours before the seizure and gradually increases to reach its maximum a few hours before the seizure. 2. In the few minutes that immediately precede the seizure there is a rapid decrease of the alkali reserve which reaches a normal value. 3. During the convulsive seizure the alkali reserve appears normal and remains so until the onset of a new attack. 4. The urinary hydrogen ion concentration behaves in the same way as the alkali reserve. However, the fluctuations between high and normal values are not so pronounced as for the alkali reserve. 5. The facts mentioned prove that convulsive seizures coincide with the moment when there is a rapid acid inflow into the circulation of the blood which results in a lowering of the alkali reserve with a probable increase of calcium in the blood plasma. These facts contrast with what has generally been admitted heretofore. 6. It is therefore admissible to think that convulsive seizures in epileptic persons are preceded by phenomena of a disturbed acid-base equilibrium in the tissues, as proved by the modifications of the blood plasma, which presumably are related to the pathologic condition.

FERRARO, New York.

THE WARTENBERG PYRAMIDAL TRACT SIGN. K. ZINNER, Arch. f. Psychiat. **92**:411, 1930.

The pyramidal tract sign was described by Wartenberg in 1927. It consists in flexion, adduction and opposition of the thumb when the four fingers are made to flex against resistance. When the movement of the thumb contains all three of the components mentioned, the sign is of pathologic significance.

In the present paper Zinner reports a study of a number of cases of pyramidal tract lesions in normal children, from 2 weeks to 17 years of age, and in normal adults. He also introduces a modification of the reflex, which consists in eliciting the movements of the thumb when only the index finger is made to flex against resistance. He finds that the sign is of significance only when all three components of the movement are present, the most important being the opposition of the thumb against the hand. He finds that in children this sign is positive up to 9 months of age; from then on to the age of 2 years it loses its constancy, and is usually found only on one side, whereas after the second year it is not found at all.

The Wartenberg sign is found frequently in disease of the pyramidal tract. The modification introduced by the author is even more frequently observed.

Post mortem, in cases in which there was some disturbance of the pyramidal tract, the thumb may assume the Wartenberg position.

MALAMUD, Iowa City, Iowa.

ARTHRITIS DEFORMANS AS A CAUSE OF "ISCHIAS" AND "MERALGIA PARESTHETICA." W. FÜRNROHR, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:68, 1930.

It is well known that severe forms of arthritis deformans produce various forms of nervous disturbances, such as root pains and intercostal, brachial and crural neuralgias. Fürnrohr believes that the milder forms of this disease produce symptoms more frequently than is realized. He points out one feature that distinguishes true sciatic pain from sciatica; namely, that stretching the sciatic nerve causes pain in true sciatic neuritis and not in sciatica. On the contrary, flexion of the leg causes pain in the latter. The x-rays show changes in the vertebrae and femur even in the milder cases. The vertebrae show spurs, especially on their lower borders, and the femur is rounded off, while the trochanter shows small deposits. How is it that with such mild changes there should be a picture of sciatica? Fürnrohr believes that as a result of the arthritis there result pains which, while not truly sciatic, radiate in the distribution of this nerve. He thinks that the pain is due, in the later stages at least, to a narrowing of the intervertebral foramen with compression of the nerve root. Fürnrohr reports a case of meralgia paresthetica which showed arthritic changes in the acetabulum and head of the femur; he believes that these were responsible for the clinical picture.

ALPERS, Philadelphia.

SULPHUR, TURPENTINE AND ALEPOL INJECTIONS IN PERSISTENT PSYCHOSIS. DUNCAN MACMILLAN and ANDREW MCNAE WYLLIE, Lancet **1**:909 (April 25) 1931.

A series of sixty-one patients with persistent psychoses were treated with repeated intramuscular injections of 1 per cent sulphur in olive oil, turpentine or a chaulmoogra oil preparation. A review of the results as a whole showed no correlation between the physical disturbance produced and the mental changes. A marked and constant increase in the leukocytes was produced by the sulphur, while only a slight increase occurs after injection of turpentine and a chaulmoogra oil preparation. Despite the fact that sulphur was capable of stimulating a vigorous leukocytic response, it did not produce a corresponding mental improvement. Therefore, it is evident that the stimulation of the defense mechanism of the body as indicated by leukocytosis is not the essential factor in effecting mental improvement. Sulphur, furthermore, was found to be an excellent agent for the artificial production of pyrexia. Yet, but little beneficial effect occurred from it. It is the opinion of the authors that pain and the necessary increase of nursing attention are the most important factors in the improvement in some of the cases because they keep the patient more closely in contact with his environment.

BECK, Buffalo.

VISUAL HALLUCINATIONS IN PATIENTS WITH OPHTHALMIC PATHOLOGY. A. TERSON, Ann. d'ocul. **167**:815 (Oct.) 1930.

Visual hallucinations, like all other sensory hallucinations, affect many patients who have no ocular lesions or lesions of other sense organs. In cases in which this is not true one should question whether the eye gives rise to the visual representations. Terson concludes by saying that he admits the eye as a direct cause of visual hallucinations only with extreme reserve. Hallucinations, either lilliputian or of various other types, are exceptional in a patient with diseases of the eye. If they do occur, they assume the same form as those noted in subjects with cerebral lesions. It is the same with other sensory hallucinations; they usually occur whether the nose, ears or tongue are normal or pathologic. If the ocular or orbital origin

of visual hallucinations were a factor, these phenomena would be frequently noted. Ocular infections, operations and traumatism seldom cause these phenomena. Postoperative delirium is only noticed after prolonged closure of both eyes. In intracranial lesions, especially tumors, when the optic tract or the occipital and temporal lobes are involved, visual hallucinations are frequently noticed and are often a valuable localizing sign in diagnosis. If visual hallucinations do occur in conjunction with diseases of the eye there is usually coexisting cerebral disease.

BERENS, New York.

THE BEHAVIOR OF PULSE RATE, PULSE VOLUME AND BLOOD PRESSURE NORMALLY AND UNDER THE INFLUENCE OF DIATHERMY ON THE BRAIN IN NORMAL AND IN CATATONIC PERSONS. H. SCHMID, Arch. f. Psychiat. **92**:663, 1930.

Two normal persons and five catatonic patients were used in the experiments. All were subjected to diathermy of the head for thirteen minutes, the pulse rate, pulse volume and blood pressure being determined before and after the diathermy. The results were as follows: Both the normal persons and the catatonic patients reacted to this stimulation. In normal persons there was a moderate increase of the pulse rate during and a short time after the diathermy. There was a moderate drop in the arterial blood pressure, with a definite increase of the pulse volume. These changes disappeared completely at the end of the hour. In catatonic patients, the responses were much less consistent, so that the reactions even in the same patient differed at different times. There was also an increased irritability and lability of the whole circulatory apparatus. This showed itself in the occurrence of fluctuations in blood pressure and pulse, even before the beginning of the diathermy. At the end of the experiment the values did not return to normal.

MALAMUD, Iowa City.

FURTHER NOTES ON EXAMINATION OF CEREBRO-SPINAL FLUID BY ULTRA-VIOLET LIGHT. E. F. SKINNER, J. Neurol. & Psychopath. **11**:144 (Oct.) 1930.

A second and more comprehensive study of the absorption of ultraviolet rays by the cerebrospinal fluid is presented. This paper is more valuable and convincing than the first because the usual spinal fluid examinations are recorded in each case along with the spectroscopic picture. A striking observation is that neither the cell count nor the absolute protein content is responsible for the reaction. A case of dementia paralytica in which the pleocytosis and protein are increased to about the same degree as they are in a case of tuberculous meningitis gives thoroughly different spectroscopic features. Skinner feels convinced, therefore, that the absorption depends on some undetermined physical factor in the spinal fluid. He believes that this phenomenon, as well as the colloidal gold curve, depends on similar though not identical variations in the surface charges of particles of colloid. The author concludes that formerly he has stressed too much the individuality of the spectrogram in the conditions he studied. The amount of absorption, on the other hand, is much more valuable in reference to recoverability in the cases of meningitis than it is to identify the etiologic type.

BECK, Buffalo.

OBSERVATIONS ON HUMAN TETANY. H. A. SALVESEN, Acta med. Scandinav. **73**:511, 1930.

In five cases of tetany after strumectomy in females only one patient died a few months after the operation. The other four have lived from three to four years. The administration of calcium chloride by mouth completely sufficed to remove all symptoms of tetany. Two different states, however, can develop. In the first instance the blood calcium may be retained almost at a normal level through calcium administration and tetany may appear as soon as calcium administration is stopped and the blood calcium content allowed to sink to 7 mg. per

hundred cubic centimeters. In the second instance the organism becomes accustomed to a lower blood calcium content, even to the level of 500 mg. per hundred cubic centimeters. In this case tetany still remains absent but cataract may develop. In one patient ultraviolet rays caused a rise in the blood calcium. A considerable difference between the calcium content of the plasma and that of the serum could not be determined in one case of spontaneous tetany with chronic insufficiency of the parathyroid.

HART, Greenwich, Conn.

THE LABYRINTH OF BUFO VULGARIS JAPONICUS LARVA. ESPECIALLY, UPON THE MORPHOLOGIC STUDY OF THE PERILYMPHATIC SPACE, IN CONNECTION WITH THE MEMBRANOUS LABYRINTH AND AUDITORY CAPSULE. KAGEYAS W. AMANO, J. Morphol. & Physiol. **51**:207 (March 5) 1931.

The perilymphatic space of Bufo vulgaris japonicus starts its development with the chondrification of the auditory capsule, and is completed by the end of the first third of metamorphosis. The author divides the whole spatium into two parts: the ductus perilymphaticus et diverticula and the pars spongiosa spati perilymphatici. The ductus perilymphaticus et diverticula may play an important rôle in carrying out the functions of both equilibrium and audition. The pars spongiosa serves not only to fasten the membranous labyrinth to the capsular wall, but acts as a safeguard for the functions of both the membranous labyrinth and the ductus perilymphaticus et diverticula. The ductus system may have more important physiologic relations than does the membranous labyrinth in connection with the cranial cavity and spinal cord as to the change of pressure, the transmission of vibrations, the osmosis of fluids, etc.

WYMAN, Boston.

MYOTONIA CONGENITA IN TWO SIBLINGS. K. MOË, Norsk mag. f. lægevidensk. **91**:1392 (Dec.) 1930.

Two cases of myotonia congenita in siblings, in a boy aged 5½ and a girl aged 1½ years, are described. They showed hypotonic paresis of the muscles of the lower extremities in the gluteal region with absence of tendon reflexes. The muscles since birth had been deformed, weak and toneless; in the early stages of childhood walking and standing were impossible, and movements in bed alone could be carried out. No progession of the disease was noted. The arms were not affected. The muscles of the neck and lips were somewhat atrophic. Sensibility was retained. Gradually the children learned to do a little walking and standing. The author differentially diagnoses this condition from the Werdnig-Hoffman disease by the absence of atrophy in the lower extremities and of progression. However, other phenomena such as the familial involvement tend to support Wallgreen's conception of the identity of the two diseases.

HART, Greenwich, Conn.

THE DIFFICULTIES OF DIFFERENTIAL DIAGNOSIS BETWEEN THE HYPERTENSIVE FORM OF ENCEPHALITIS LETHARGICA AND CEREBRAL TUMOR. WORMS and SOURDILLE, Ann. d'ocul. **167**:840 (Oct.) 1930.

Worms and Sourdile report the case of a man whose condition had been diagnosed as epidemic encephalitis in 1923. The case demonstrated the difficulties in differential diagnosis between epidemic encephalitis of hypertensive form and brain tumor. In 1926, this patient had bilateral papilledema and a decompression operation was performed on account of failing vision. In 1929, following ventriculography, a tumor was removed from the left temporal lobe. The febrile onset of the condition, followed by a period of amelioration and recurrence, and improvement after treatment with methenamine caused a diagnosis of encephalitis to be made. In the absence of other clinical symptoms, the persistence of papilledema and, above all, ventriculography permitted the diagnosis of cerebral neoplasm and surgical treatment.

BERENS, New York.

CONVULSIONS DURING SURGICAL ANAESTHESIA. J. ROSS MACKENZIE, Brit. M. J. **1**:440 (March 14) 1931.

Seven cases of generalized, epileptiform convulsions occurring during ether anesthesia are reported. All occurred in young people, mostly children, on whom operations were being performed for some toxic condition, such as a suppurative appendix, etc. The convulsions usually came on about fifteen minutes after anesthesia had been begun. The author advances the possibility of three causative factors: impurities in the ether; carbon dioxide; and toxemia from acute suppuration occurring in a person whose nervous system is readily excited into abnormal activity. Of interest to the neurologist is the fact that in most of the cases, the convulsions seemed to begin in the left side of the face and then spread to the rest of the body. The treatment for the condition is to cease the administration of anesthesia and to give the patient oxygen.

FERGUSON, Niagara Falls, N. Y.

PSYCHOPATHY IN FEEBLE-MINDEDNESS. A. WIMMER, Ugest. f. læger **92**:1154 (Dec. 4) 1930.

Wimmer rightly warns against a false psychiatric terminology, particularly in civil and criminal proceedings in which psychopathy is often confused with feeble-mindedness. The latter condition is differentiated by degrees into idiocy, imbecility and "debility" (moron). Idiocy, according to the author, represents grades of intelligence from zero to 30 per cent of normal, imbecility grades from 30 to 55 per cent, and "debility" those from 55 to 75 per cent. Psychopathy is, in general, a constitutional deficiency which shows itself chiefly in abnormal feeling and behavior reactions, without actual defect in intelligence. It comprises peculiarities of character and variations of reaction more than anomalies of understanding and comprension. Although psychopathic persons may have weakness of judgment dependent on false representation and feeling reactions, this weakness is purely secondary to an affective deficiency.

HART, Greenwich, Conn.

THE TREATMENT OF CHOREA WITH PHENYL-ETHYL-HYDANTOIN. J. D. PILCHER and H. J. GERSTENBERGER, Am. J. Dis. Child. **40**:1239 (Dec.) 1930.

Crystals of phenyl-ethyl-hydantoin, sold under the name of "nirvanol," were used by Pilcher and Gerstenberger in the treatment of fifteen cases of chorea. The single dose varied from 1 to 3 grains (0.065 to 0.195 Gm.) according to age, and this was repeated three times a day until a well developed rash occurred; in six cases there was no rash and the use of the drug was stopped after fifteen or twenty days. Seven of the nine patients in whom a rash appeared had fever. After withdrawal of the drug, the rash and fever subsided. Of the seven patients who reacted with fever and rash, five showed prompt improvement with the appearance of the exanthem. Pilcher and Gerstenberger conclude that phenyl-ethyl-hydantoin is beneficial in severe cases of chorea, and that this benefit is indicated by the appearance of a fever and a morbilliform rash.

DAVIDSON, Newark, N. J.

A CASE OF ALTERNATE HEMIANESTHESIA. DIVRY, J. de neurol. et de psychiat. **31**:73 (Feb.) 1931.

The author presents the case of a man, aged 72, who seven years before had had an attack in which he became semicomatose, and the following day noted paralysis of the left arm and the left side of the face. The left faciobrachial monoplegia improved until there was only a slight weakness, but there later developed an alternate hemianesthesia of the syringomyelic type, accompanied by some ptosis of the left upper lid and contraction of the pupil. The author considers it difficult to explain the symptoms on the basis of one lesion. The monoplegia and facial paralysis he considers as a manifestation of a cortical lesion, the other symptoms being explained on the basis of a lesion of the brain stem. Because

of the age of the patient, the author supposes that the pathologic process is in the nature of softening following hemorrhage or arteriosclerotic changes.

WAGGONER, Ann Arbor, Mich.

BLOOD PRESSURE BEFORE AND AFTER OPERATION IN HYPERTHYROIDISM. LEWIS M. HURXTHAL, Arch. Int. Med. **47**:167 (Feb.) 1931.

Routine blood pressures were taken in patients with hyperthyroidism before and after operation. Hurxthal could find no definite relation between the blood pressure and the basal metabolic rate at these times. Following subtotal thyroidectomy, there was a slightly lower basal systolic pressure and an increased diastolic pressure in the majority of the cases. The average basal systolic pressure in patients with adenomatous goiter who had been relieved by operation was higher than in those with the exophthalmic type, due to higher age incidence in the former group. The basal blood pressure after operation in cases of toxic goiter closely parallels that in the nontoxic group before operation. Thyroidectomy causes no appreciable difference in basal blood pressure in persons with hypertension. From this study there is no proof that hyperthyroidism causes permanent hypertensive cardiovascular disease.

DAVIDSON, Newark, N. J.

THE DISTRIBUTION OF THE BRANCHIAL NERVE IN MYTILUS EDULIS AND ITS RELATION TO THE PROBLEM OF NERVOUS CONTROL OF CILIARY ACTIVITY. ALFRED M. LUCAS, J. Morphol. & Physiol. **51**:195 (March 5) 1931.

The branchial nerve and its branches, which are limited altogether to the tissue suspending the gills, transmit their fibers through the interconnective tissue matrix to the epithelium. Apparently, most of the epithelium, as well as two sense organs, the osphradium and the abdominal sense organ, are well supplied with nerves. This, coupled with the nearly complete absence of muscles, indicates that the function of the branchial nerve is mostly, if not entirely, sensory. Although the branchial nerve lies close to the gills, it does not send branches to that organ, and so obviously cannot innervate its ciliated epithelium. The ciliated epithelium is not the only contractile organ of the gills that must function without central control, for muscles that extend across the blood spaces have been described. The gills, therefore, may be autonomous organs.

WYMAN, Boston.

AN INVESTIGATION INTO A POSSIBLE NERVOUS MECHANISM INVOLVED IN THE LIBERATION OF HISTAMINE. R. G. MACGREGOR and S. PEAT, J. Physiol. **71**:31 (Jan.) 1931.

The significance of the relatively large quantities of histamine in extracts of lung tissue compared with extracts of other tissues found by various workers is as yet not understood. In view of the work of Lewis and Marvin, which indicates that the vasodilatation caused by antidromic impulses is due to the release peripherally of a histamine-like substance, the possibility of the histamine content of the lungs being controlled by a nerve mechanism was suggested. Macgregor and Peat, using a technic by which it is possible to estimate a difference in the histamine content of the lung of 20 per cent or more, found that neither stimulation of the nerves supplying the lungs nor perfusion with epinephrine, pilocarpine or physostigmine gave rise to any detectable change in the histamine content.

ALPERS, Philadelphia.

HERPES ZOSTER DURING ARSPHENAMINE THERAPY. J. L. WOLLHEIM, Am. J. Syph. **15**:90 (Jan.) 1931.

In arsenic poisoning the central nervous system is involved more severely than any other tissue of the body. Arsphenamine and neoarsphenamine can produce such poisoning in susceptible persons, and herpes zoster is one of its commoner

manifestations. The author presents three cases of newly acquired syphilis; in two of these patients herpes zoster developed after eight injections of neoarsphenamine, and on the third a painful rash appeared after only six injections. The cutaneous lesion cleared up after treatment with arsenic had been temporarily discontinued; the blisters were dressed with methyl salicylate and collodion 5 per cent. After recovery from the herpes, treatment with arsphenamine was resumed without any recurrence of the cutaneous lesion. It is not necessary to suspend administration of mercury or bismuth during treatment for herpes.

DAVIDSON, Newark, N. J.

TUMORS OF BRAIN STEM. CLINICAL STUDY OF FIVE CASES WITH AUTOPSY FINDINGS. S. BROCK and W. NEEDLES, J. Nerv. & Ment. Dis. **72**:521 (Nov.) 1930.

The authors present five cases of brain stem tumors with the object of analyzing the diagnostic difficulties. In two cases a condition of seemingly unrelated muscular atrophy obscured the clinical picture. The acute onset and remission in three cases pointed away from neoplasm and seemed to emphasize the diagnosis of multiple sclerosis and epidemic encephalitis. In one case, Argyll Robertson pupils focused attention on cerebral syphilis. The absence of choked disk throughout the course of two cases and the dyskinetic and behavior disturbance with unusually rapid terminal decline were additional confusing elements. In tumors of the brain an acute onset may mislead one. In the undiagnosed cases aid might have been rendered by findings of ventriculography.

HART, Greenwich, Conn.

AMBULATORY AUTOMATISM IN HYPERTONIC ENCEPHALITIS. A. LEROY, J. de neurol. et de psychiat. **31**:111 (Feb.) 1931.

The author reports the case of a woman, aged 33, in whom a depression developed following the onset of symptoms suggesting a "hypertonic encephalitis." This depression was evidenced by attempts to commit suicide and a mental and emotional reaction of depression. In addition to these symptoms, attacks developed during which she would run, leap over beds and occasionally fall down. During the course of the attacks her eyes were staring, and she seemed to be frightened and irresponsive to stimuli. The author notes that the father of the patient was a confirmed alcoholic and that a brother and a sister were epileptic. The author refers to several cases reported in the literature of the association of epileptic-like seizures with postencephalitic states.

WAGGONER, Ann Arbor, Mich.

STUDIES IN BROMIDE DISTRIBUTION IN THE BLOOD. I. IN VITRO EXPERIMENTS OF BROMIDE AND CHLORIDE DISTRIBUTIONS. A. BAIRD HASTINGS and H. B. VAN DYKE, J. Biol. Chem. **92**:13, 1931.

The conclusions reached by the authors are: 1. When bromide is added to blood in vitro it distributes itself in such a way that the distribution ratio between cells and serum is about 10 per cent higher than the corresponding chloride ratio. 2. It seems to be freely diffusible from cells into serum or from serum into cells. 3. If the p_H of the serum of bromide-containing blood is altered, the distribution ratio changes in a direction and in an amount corresponding to that predicted by the Donnan equilibrium; i. e., a higher p_H leads to a lower ratio. 4. If blood containing bromide is oxygenated and reduced, the bromide distribution ratio changes in a manner consistent with that expected of diffusible ions; i. e., reduction of blood leads to a higher ratio.

FREMONT-SMITH, Boston.

JUVENILE DEMENTIA PARALYTICA AND COMBINED SCLEROSIS OF THE MEDULLA. LARUELLE and HEERNU, J. de neurol. et de psychiat. **31**:106 (Feb.) 1931.

The authors present the case of a girl, aged 17, who showed psychic disturbances of general paralysis, which had developed at the age of 14 and were progressive.

She showed neurologic evidence of pyramidal tract involvement with a positive Babinski sign on both sides, with normal knee jerks and a suggestion of tabes dorsalis in the loss of achilles jerks. The syphilitic nature of the involvement was substantiated by the presence of Argyll Robertson pupils and by positive serologic tests. The interesting feature of the case is that the authors conclude that it is a symptom complex of hereditary syphilis.

WAGGONER, Ann Arbor, Mich.

THE CLINICAL FORMS OF ACUTE NIGHT BLINDNESS ETIOLOGICALLY CLASSIFIED. H. LAGRANGE, Ann. d'ocul. **167**:652 (Aug.) 1930.

Lagrange points out that acute night blindness has been associated with xerosis of the conjunctiva since it was first described. He refers to the work of Goldsblatt and Soames, who showed that the liver plays an important rôle in storing fat-soluble vitamin A. These experiments were carefully verified by Wagner, who stated that the lack of vitamin A in children suffering from diseases of the liver quickly produced signs of keratomalacia. This condition readily responds to cod liver oil. He also speaks of night blindness in general diseases, and considers the question of scurvy and infectious diseases, stressing the important rôle of vitamins in this condition.

BERENS, New York.

DELINQUENCY AND THE FLORENTINE COURT RECORDS OF BENVENUTO CELLINI, AS RECONSTRUCTED IN THE LIGHT OF THE LEGAL CODE OF HIS TIME AND OF RARE UNPUBLISHED DOCUMENTS. LUIGI GRECI, Arch. di antropol. crim. **50**:342 and 509, 1930.

This is a long historical and criminologic essay on the noted figure of the Italian renaissance. Only in the light of the moral and juridical code of his time may one come to an adequate appreciation of this delinquent genius. Referring to the conditions of communal life and to the social psychology of the first half of the sixteenth century, the author gives a detailed analysis of the crimes committed and the punishments imposed. The work is not suitable for abstraction, but rather requires a critical review; those interested should read it in the original.

YAKOVLEV, Palmer, Mass.

THE COMPARATIVE ANATOMY OF THE SO-CALLED ACCESSORY ABDUCENS NUCLEUS. T. NAKAMURA, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:262 (Oct.) 1930.

Anatomic studies of this nucleus were made on *Homo sapiens, Pitheci, Prosimii, Chiroptera, Carnivora, Pinnipedia, Insectivora, Rodentia, Ungulata, Natantia, Edentata, Marsupialia* and *Aves*. No relationship could be found between it and the abducens. The form of the cells as well as their position showed a definite relationship between this nucleus and the root fibers of the facialis, and the author is therefore inclined to regard it as an accessory nucleus of the facialis, which may perhaps have vegetative functions.

KESCHNER, New York.

SUICIDE BY MEANS OF THE INGESTION OF A FLUORINE COMPOUND. ADAMO BOCHKOR, Arch. di Antropol. crim. **50**:570, 1930.

A boy, aged 15, intentionally absorbed the contents of a glass bottle. He fell, had hiccups, complained of pain in the throat and stomach, and died half an hour later. The inside of the bottle was found to be covered with a film of paraffin. This fact and the observations at autopsy led to the conclusion that the contents of the bottle had a strong corrosive property. Chemical analysis of the contents of the bottle and of the stomach revealed the presence of fluoride of ammonium. The author quotes five cases of poisoning with fluorine compounds and summarizes the toxicology and pathologic changes.

YAKOVLEV, Palmer, Mass.

A Case of Taboparesis Treated by Hyperpyrexia Induced by Hot Baths. C. R. Gibson and R. G. Gordon, Brit. M. J. **1**:1015 (June 13) 1931.

A patient, with unmistakable signs of the tabetic form of dementia paralytica, who showed marked neurologic and mental symptoms, was given forty-one treatments in a hot bath varying in temperature between 106 and 110 F. The duration of each treatment in the bath averaged from fifty-two to fifty-three minutes. The patient was then wrapped in blankets and made to rest for from one and a half to two hours. The first treatment was given on April 29, 1930, and the last on April 6, 1931. During this period the patient's symptoms, neurologic (except tendon reflexes) and especially mental, showed marked improvement. The Wassermann reaction was unaltered; the gold curve changed from 0000114433 to 4444332000.

Ferguson, Niagara Falls, N. Y.

Guides to the Prevention and Treatment of the Simpler Neuroses. Maurice Fremont-Smith, Am. J. M. Sc. **182**:261 (Aug.) 1931.

The author thinks that the internist alone is privileged to consider his patient as a whole. Simple concepts are presented in order to facilitate the internist's approach to the patient with a neurosis. Various types of emotional difficulty with resulting symptoms should be reviewed for the patient. Difficulties in child training, parental guidance, marriage and sex instruction are discussed. An attempt should be made to make the patient aware of the fear or the subconscious conflict that is responsible for his own difficulty.

Michaels, Detroit.

Alexia and Agraphia of Evolution. A. and J. Ley, Encéphale **26**:429 (June) 1931.

This article is a study of six patients, ranging in age from 8 to 14 years, all of whom showed more or less specific disturbances in reading and writing capacities. Each case is summarized. All showed a tendency to improve with age, leading to the designation: "agraphia and alexia of evolution." The improvement, however, was very slow and caused these patients to stand out in contrast with the normal children. On gross examination, much of this is passed by; on careful testing, a paralexia and agraphia will be discovered. The latter often persists after disappearance of the former, indicating the independence of the two processes.

Anderson, Los Angeles.

The Light Reflexes from the Membrana Limitans Interna of the Retina. Lijo Pavia, Ann. d'ocul. **168**:281 (April) 1931.

In studying the light reflexes from the membrana limitans interna of the retina, Lijo Pavia has noted that these reflexes disappear under certain conditions and reappear at other times, usually on improvement of the pathologic condition. He has noted a complete absence of the light reflex in all patients who have increased blood sugar. He reports the case of a patient, aged 11, who received a penetrating wound of the left eyeball. He studied the return of the light reflexes in the retina with the improvement in the condition of the retina, and points out the fact that these reflexes may be well studied by means of fundus photography.

Berens, New York.

The Problem of Mental Disease and Delinquency in the Adolescent. Michael Osnato, J. Nerv. & Ment. Dis. **74**:11 (July) 1931.

The influence of environmental factors in the causation of adolescent mental disease becomes increasingly evident as one's experience grows. A series of graphically narrated cases of psychoses and delinquency in adolescents is presented by the author as illustration of parental, religious and other factors. The breaking

down of religious belief without the replacement of anything higher is an important factor in many cases. Interference with the normal flow of sexual energy, producing repression and regression, produces serious behavior disturbances. The study of the mechanism motivating the behavior of delinquent and neurotic children is then stressed by the author.

HART, Greenwich, Conn.

TREATMENT OF DISSEMINATED SCLEROSIS BY LIVER. ALEXANDER GOODALL and JAMES K. SLATER, Brit. M. J. **1**:789 (May 9) 1931.

The authors report the results in five cases of disseminated sclerosis with treatment by the ingestion of whole liver (½ pound daily, lightly cooked). The observations cover a period of seven months. Remarkable improvement occurred in every case. Promising results are stated to have been obtained in later cases. Cognizance is taken of the fact that disseminated sclerosis is a notoriously difficult disease in which to assess treatment, yet it is highly improbable that all results could be due to remissions. It is suggested that disseminated sclerosis may be another of the deficiency diseases.

FERGUSON, Niagara Falls, N. Y.

NEUROHYPOPHYSIS AND ERECTION. G. ROASENDA, Riv. di pat. nerv. **37**:75 (Jan.) 1931.

The author reports the clinical history of a syphilitic patient suffering from incontinence and absolute loss of sexual stimuli and erection for almost two years. The author tried several pituitary preparations and found that solution of pituitary (Parke Davis) had an immediately beneficial effect in the reestablishment of the bladder function and immediate erection after every injection. Later, the sexual function gradually returned to normal. The author is inclined to believe that the solution of pituitary acted on the sympathetic hypogastric plexus and directly on the unstriped musculature of the bladder and of the cavernous bodies.

FERRARO, New York.

A STUDY OF THE RETINAL BLOOD PRESSURE IN PATIENTS WITH GENERAL ARTERIAL HYPERTENSION. R. BIDAULT, Ann. d'ocul. **168**:255 (April) 1931.

From a study of the retinal blood pressure in patients with increased general arterial pressure, Bidault concludes that a relative increase in pressure in the retinal arteries is noted constantly in patients with general hypertension; the increase is most marked in patients who have marked hypertension. He was, however, unable to draw any clinical conclusions from his observations. He noted a constant increase in retinal pressure in patients with marked hypertension when this was accompanied by changes in the retinal blood vessels or other retinal complications of arterial hypertension.

BERENS, New York.

VALIDITY OF THE ALL-OR-NONE LAW. G. MANSFELD and K. HECHT, Arch. f. d. ges. Physiol. **227**:797, 1931.

If one stimulates the chorda tympani with stimuli of different strengths, one finds even after the weakest stimuli an increased activity of all the acini of the glandula submaxillaris; after strong stimulation the acini show a more marked increase of activity, but there is no increase in the number of the stimulated acini. In other words, an increase in the stimulus does not increase the number of the excited nerve fibers, but the degree of stimulation of the fibers in the chorda, and the all-or-none law does not seem valid any more for the peripheral nerve fibers.

SPIEGEL, Philadelphia.

THE LYMPHOCYTE REACTION IN THE BLOOD PICTURE OF SYPHILIS AND METASYPHILIS, AND ITS SIGNIFICANCE FOR PATHOGENESIS AND THERAPY. W. SKALWEIT, Ztschr. f. d. ges. Neurol. u. Psychiat. **129**:376, 1930.

The blood picture in syphilis and metasyphilis shows a characteristic difference in the lymphocyte content. In syphilis the lymphocytes average 35 per cent, whereas in dementia paralytica they average 20 per cent. There is, therefore, a decreased reaction capacity in dementia paralytica. In cases of dementia paralytica in which the patients are treated with malaria, the lymphocytes increase in number.

ALPERS, Philadelphia.

INDEX OF CELEBRATED CASES. G. E. WIRE, J. Am. Inst. Crim. Law & Criminol. **21**:339 (Nov.) 1930.

To a reader interested in detective, legal, medical or the purely literary side of crime, this index unlocks many an interesting case. The index and explanatory notes should be of importance to psychiatrists who are called on to examine individual motives in criminal acts, or to study the individual criminal. The dictum that "truth is stranger than fiction" would seem to hold particularly true in the field of criminology.

WILLEY, Albion, N. Y.

A CASE OF BILATERAL HEMIANOPIA WITH CONSERVATION OF MACULAR VISION. J. PALLARÉS, Ann. d'ocul. **168**:45 (Jan.) 1931.

In the case of a boy, aged 16, seen by Pallarés, the diagnosis was bilateral hemianopia with preservation of macular vision, caused by an injury at birth from the use of forceps. The labor had lasted eighteen hours in spite of several attempts at instrumental delivery. The patient was born asphyxiated and had an enormous epicranial hematoma. He weighed 6,000 Gm. Visual acuity was improved by galvanization.

FALSE GLAUCOMA. E. AUBINEAU, Ann. d'ocul. **167**:550 (July) 1930.

De Wecker, in 1896, described false glaucoma as atrophy of the optic nerve with excavations but not accompanied by hypertension. After reporting two cases of this character, Aubineau concludes that he agrees with Morax and Bailliart that there is an atrophy of the optic nerve with excavation which should be distinguished from glaucomatous excavation. Decompression operations are contraindicated in this condition.

THE EFFICACY AND DIAGNOSTIC IMPORTANCE OF THE VASODILATORS IN ANGIOSPASM OF THE RETINAL ARTERY, WITH SPECIAL REFERENCE TO ACETYLCHOLINE. S. MARTIN, Ann. d'ocul. **168**:102 (Feb.) 1931.

The author points out that many of the cases of so-called embolism of the central artery are really due to angiospasm, which may continue for a long time and result in a partial loss of vision. He found that atropine improved the vision in some cases, and in others in which atropine failed to dilate the vessels acetylcholine gave remarkable results.

EXOPHTHALMOS FROM TUMOR OF THE FRONTAL LOBE. F. TERRIEN, SAINTON and P. VEIL, Ann. d'ocul. **167**:845 (Oct.) 1930.

Terrien, Sainton and Veil report the case of a patient who had exophthalmos secondary to a tumor in the frontal lobe. The tumor was situated in the right frontal lobe and had destroyed the roof of the right orbit.

BERENS, New York.

Society Transactions

GERMAN NEUROLOGICAL SOCIETY

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O. FOERSTER, M.D., *President*

DEUTSCHE ZEITSCHRIFT FÜR NERVENHEILKUNDE **115**:147, 1930; **116**:2, 1930.

DR. W. J. BERNIS, Rochester, N. Y., *Abstractor*

DEGENERATION AND REGENERATION OF THE PERIPHERAL NERVOUS SYSTEM.

DR. J. BOEKE, Utrecht, Holland.

1. *The Conducting Element of the Nervous System, Neurofibrils and Neuroplasma; the Synapse.*—In studying the manifestations of degeneration and regeneration of the peripheral nervous system, as observed with the prevailing staining methods, it is of fundamental importance to be clear in one's mind whether the experiment attempts to establish a system that plays an important part, a subordinate mechanical function or merely a trophic function. Some even question the existence of neurofibrils in the living protoplasm.

According to one conception, represented by Max Schultze and refuted by Apathy and Bethe, the neurofibrils are the only exclusive conducting mediums of the nervous system. Another conception, represented by Stöhr, assigns this function to the neurofibrils as well as to the surrounding interfibrillar and perifibrillar substance. A third group of investigators, M. Wolff, Schäffer, Strasser and Verworn, are of the opinion that the neurofibrils are not themselves the transmitting substance, but rather are to be considered as a support of the stimuli-transmitting axis hyaloplasm, or as possessing a trophic metabolic function. According to others, they are entirely absent in living cells and nerve fibers. With dark-field illumination, Levi found no neurofibrils in the growing nerve processes of cultures in vitro. He observed only a general "glitter" of the neurites. Likewise, Matsumoto, after most careful observation, could find no neurofibrils in the living nerve processes in cultures in vitro, while after fixation they appeared clearly in the spinal as well as in the sympathetic elements. Lewis stated, after repeated examination of living fibers with bright and dark-field illumination, that he was unable to detect neurofibrils, and came to the conclusion that they are probably due to the peculiar manner in which the homogeneous cytoplasm coagulates. De Reneyi and Peterfi met with the same experience.

Are the neurofibrils therefore to be considered as mere artefacts that do not exist in the living tissue? According to Boeke, they are positively present in the living protoplasm; he refers to his work on this subject published in 1926 and 1929. Apathy, and later Goethlin, in an extensive investigation of the relation of neurofibrils in polarized light have unmistakably proved their presence in the living nerve processes in suitable objects in both nonvertebrate and vertebrate animals. Bozler (1927, 1928) described similar observations in the ganglion cells and fibers of Rhizostomea. Hesse, in 1895, observed the same in the living object.

Accepting that neurofibrils exist in the living elements, the question arises as to what is their function. Von Lenhossek said that the neurofibrils, in the first place, are a supporting structure, not to the fully developed nerve elements but in their development. The primary function is not to hold and give support to the developed neuron, but rather to give strength and energy to its development and growth. That it does not disappear after the development of the neuron can be

explained, first, by the necessity of a preparedness of the neurons, in certain cases, to regenerate according to the type of embryonic development; second, from the fact that the neurofibrils at first also have an influence over nervous activity, and in addition, from their consistency, are able to act as a supporting structure to the neuron. However, it still remains difficult to understand why so complicated a system should possess a mere mechanical function in the developed nerve fibers. The criticism of Bethe's experiments on the rate of transmission of the abdominal ganglionic chain in leeches as a proof of the transmission ability of the neurofibrils is, according to Boeke, unjustified. Jenkins and Carlson's experiments, as well as those of Parker on the snail and the earthworm, which are quoted as disproving Bethe's contention, fail to take account of the differences in the relation of the neurofibrils in the nerve fibers between the leech and the snail. Bethe's experiments contain by far too many uncontrollable factors to be considered as proving that the neurofibrils are exclusively conductive. However, among other arguments it possesses value, and it must be assumed that there is a kind of an interchange effect between the neurofibrils and the surrounding protoplasm in stimulation and the transmission of stimuli. Bethe, however, is entirely correct when he says that in the function of the neurofibrils, stimulation and transmission may well be combined with a mechanical support; but, on the other hand, when one considers the fineness of the neurofibrils and their arrangement and place in the cells in some cases, it is questionable whether the function is entirely mechanical.

According to Parker, the importance of the neurofibrillar structure is to be sought in the metabolic process and not in the transmission of stimuli. The neurofibrils in the cells are present where the metabolic processes are strongest, in the neighborhood of the nuclei, etc., and not in the places where one would look for the transmission of stimuli. It may be asked what Parker means when he says that the route of the impulse in the cells is entirely different from that of metabolism. The stimulus, the stimulus transmission and especially the physiologic elaboration of the impulses must always be localized in the ganglion cells. When he says that in the unipolar ganglion cells of vertebrates the metabolic processes come from the ganglion cell body while the stimulus impulses, on the other hand, follow the route of a nerve process, it can be argued in the first place that there is no proof of such an assertion and again that it does not disprove the conduction function of the neurofibrils; for even if a part of the stimulus impulse should follow the shortest route, since part of the neurofibrils may pass over directly from one process to another, it does not at all affect the conducting function of the central part of the process and of the neurofibrillar structure within the cell body; for it is certain that even in the cell body of pseudo-unipolar cells the impulse is being elaborated.

According to Boeke, the neurofibrils, like other differentiated protoplasm and all living substance, surely partake in the metabolic process of the living cell; assuredly, however, they also partake in the conductivity process of the nerve stimuli within the cell and axis cylinders together with the surrounding neuroplasm.

The ability of nerve elements to transmit stimuli in a definite direction depends on the differentiation of protoplasm in lineally directed parts, the neurofibrils and the neuroplasmic layer surrounding each fibril. Without the neurofibrillar differentiation it is impossible to think of a definite ordinated nervous conduction. Following this conception one is justified in studying the regeneration of the nerve elements by neurofibrillar methods of staining and in utilizing the results for physiologic conclusions.

A short reference is in order concerning the "synapse," since the conduction ability of the neurofibrils is closely connected with this question. As is known, the conception of "synapses" was first introduced by Sherrington; Foster and Sherrington considered that the conducting substance is in a fluid form, the synapse being a membranous division. In this membrane Langley localized his "receptive substance." Boeke calls attention to the fact that as long ago as 1921 he stressed that a periterminal network is to be assumed in the synapse, espe-

cially between the end-branches of the neurite and the elements that it innervates (muscle fiber, taste cell, etc.), between the neurofibril structure on the one hand and the protoplasm on the other. Lawrentjew and Stefanelli described the same thing. Cajal did not accept a relationship with the neurofibril structure. In 1929, Boeke attempted to harmonize the various concepts. He stressed the point that the synapse is not to be considered as a division between the different elements by a dead substance, but rather as connection, through a living substance, which also possesses other qualities. This guarantees the physiologic independence of the neuron and the specific nature of the synaptic connection, permits changes in the conduction ability, and explains the influence of poisons and other occurrences and the stopping of degeneration at the synapse, etc., while the continued transmission of the stimulus from the neuron to the end-organs and vice versa and the intraplasmatic position of the ends of the neurofibril structure still remains secure.

2. *Secondary (Wallerian) Degeneration.*—What happens to the axis cylinder, the myelin sheath, and the neurilemma in peripheral nerve fibers after they are separated from the ganglion cell? Does the entire axis cylinder disappear?

The problem of nerve degeneration has not undergone any change in the last few years. Since Waller's investigation it has been known that after sectioning a nerve the fibers of the peripheral end degenerate; this involves the axis cylinder as well as the myelin sheath, and they rapidly die. Here especially, however, the newer methods for staining neurofibrils have brought classification. It is now possible to study degeneration of the axis cylinder and especially of the end-organs; finally, it is chiefly the degeneration of the end-organ that controls the physiologic picture. By this method it is also possible to obtain a better insight into the manifestations of degeneration of Remak's fibers. Especially within the last few years, there has come to the foreground the problem of the degeneration of nonmyelinated sympathetic fibers and related problems of innervation.

The process of degeneration develops approximately as follows: Often after two days, and at times much sooner, it can be observed that the myelin sheath retracts; at the same time the Lantermann constrictions widen until the conical cylinder segments of the myelinated nerve fibers change into elongated drops, which undergo a further breaking down and form larger or smaller lumps and drops. At the same time, the axis cylinder becomes pale, granulates and breaks up into irregular wavy or spiral pieces, which appear in and between the fatty droplets of the myelin sheath; they break up into smaller drops and waves and finally disappear completely, so that after from fifteen to twenty days every particle of the axis cylinder has disappeared. At the same time the Schwann cells of the neurilemma become enlarged and the nuclei divide and become surrounded by a thick layer of protoplasm, so that the nerve fibers change into a thick massive granulated strand of protoplasm. At first fragments of myelin sheath are still present, but these largely disappear, partly through the phagocytic effect of the Schwann cells themselves, or combined with the aid of migrated leukocytes.

According to the investigations of Ranvier, Ströbe and Vanlair, after the fat has practically disappeared, the nerve fibers again shrink because the protoplasmic strand produced by the Schwann cells becomes narrower and vacuolated, while the nuclei diminish in size and number. The progressive vacuolation at the border of the cross-section of the fiber progresses so that the protoplasmic nerve fibers, which originally were massive, change into a more or less wide tube, intended for the reception of the newly regenerated nerve fibers. Nageotte has expressed the opinion that the proliferation of the nuclei and protoplasm does not come from the Schwann cells, but from the elements of the connective-tissue sheath (Henle's sheath), since the Schwann sheath appears to narrow down gradually into a thin strand between the protoplasmic band. Boeke cannot substantiate Nageotte's contention that Büngner's band is largely of mesodermal nature. Nageotte makes the mistake of considering not only the protoplasmic

strand lying within but also the fibrous tissue surrounding the nerve fibers as belonging to Büngner's band.

In the central stump of a severed nerve there is also a degeneration of the nerve fibers, with breaking up of the myelin sheath, which is limited to the injured part (traumatic degeneration). According to Ranvier, Engelmann and others, this breaking down extends only up to the next constriction point of the nerve fiber; according to others, the degeneration may extend to two or more segments of the nerve fibers, depending on the degree of injury sustained during the section. However, the degeneration in these cases affects the axis cylinder less than it does in the peripheral part.

According to Waller's law, degeneration of the peripheral part of the nerves is the result of separation from the trophic center of the nerve cell, the discontinuation of functional association and the interruption of conductivity. According to Bethe, this is not so. He applied ammonia to part of a nerve, and succeeded in bringing about a complete interruption of nerve conduction, which lasted longer than is necessary to bring about complete degeneration after total section. Degeneration in this case did not develop. Bethe thought that it is the local damage to the nerve that is responsible for the degeneration.

According to this conception, the degeneration must be considered as progressing centrifugally. In injuries due to toxins, in which the nerve is affected in its entire length, the degeneration, as is observed in human pathology, always sets in at the peripheral end. This would seem to be the punctum minimae resistentiae. The question arises as to why, after sectioning the nerve, the degeneration develops peripherally? If, as Bethe thinks, the degeneration is the result of a local injury, the degeneration ought to proceed in both directions with equal intensity, and not only peripherally. Also Spielmeyer, who accepted Bethe's theory, questioned this conception. But he added that so far no investigator, including himself, has brought forth a theory that explains satisfactorily the development of secondary degeneration. Boeke thinks that this problem can be explained when the following facts are considered:

In the end-organs, according to Tello (motor end-plates), the neurofibrillar apparatus especially is destroyed. Boeke has always found a similar condition in the sensory end-organs. The first changes in the motor and sensory endings in warm-blooded animals appear within from seven to twelve hours after section of the nerve. The neurofibrillar frame, in all types of endings, retains its original position within the protoplasm until it disappears entirely. The first change noticed is that the neurofibrillar frame does not take the stain well. Soon after, the pale fibrils of the frame begin to hypertrophy, to swell and partly to agglutinate, and again take a better stain. This progresses until the plate appears to be developed from thick, deeply stained neurofibrils. The shank and reticulum often remain for some time. In the next twenty-four hours, the swelling and agglutination of the frame progress; the neurofibrils fuse together; soon they break up into larger and smaller lumps and drops, and finally they melt together and gradually disappear entirely. Then there remains only the empty tactile cell, together with the nerve disk; a little later, the periterminal net, attached to the branching and end-rings of the neurofibrillar frame, also degenerates.

Many years ago, Lents and Hyelt reported on the nuclear increase in Schwann's sheath after nerve section; Büngner, in 1891, and Huber, in 1892, described the mitotic increase of Schwann's nuclei in the degenerated peripheral nerve and the formation of protoplasmic cell bands within Henle's sheath from the Schwann cells of the neurilemma. These are called Büngner's bands. Büngner was of the opinion that the cell bands in time show fibrillar streaks which are caused by the formation of new nerve fibers. The Schwann cells of the peripheral part of the nerve fiber are therefore true neuroblasts, capable of forming new nerve fibers independent of the central part. Wieting and Galeotti and Levi assumed a transformation of the Schwann cells into nerve fibers. According to Wieting, the cells in Büngner's band represent the raw material, and only through a stimulus from the central part does it become capable of conductivity.

Concerning the nature of wallerian degeneration, two questions are of fundamental importance. In the formation of Büngner's bands does the neuroplasm of the axis cylinder become destroyed together with the neurofibrils, or does the neuroplasm enter into the formation of Büngner's bands? Again, are the Schwann cells independent and in the process of degeneration are they to be considered as independent remaining cells, or during the formation of the Büngner's bands do they remain in syncitial connection? As to the second question, Boeke has already expressed his opinion.

As regards the first question, it is evident that in peripheral nerve fibers it is impossible to reach a definite decision. In the living nerve fibers, the neuroplasm optically is entirely empty and viscous. In the fixed preparation, it is exceedingly difficult to establish that the neurofibrils are really enclosed in the nuclei-stainable protoplasm.

When degeneration takes place, important changes occur in Schwann's sheath and there is a breaking up and transformation of the myelin, with a proliferation of the cells of Schwann's sheath, how can it be established with certainty that the neuroplasm as such disappears or that it partakes in the formation of Büngner's band?

Boeke's conception of secondary degeneration is that, after sectioning the entire peripheral nerve does not become destroyed; only the conducting differentiation of the nerve substance is destroyed, while the neuroplasm of the axis cylinder process together with the protoplasm of the Schwann cells form Büngner's band.

First, in successful regeneration the newly formed neurofibrils that have penetrated into the old sheaths of the peripheral nerve fibers are not found between but within the protoplasm of the bands. This cannot be denied. Cajal has conceded that within the old nerve tube the neurofibrils are found within the protoplasm of Büngner's hands. This has also been substantiated by Bielschowsky. (The author showed photomicrographs of regenerated nerve fibers to substantiate his assertion.) But if this contention is true, it follows that either the protoplasm of the sectioned nerve process fuses completely with the protoplasm of the Schwann cells, or the nerve process further proceeds within an entirely foreign protoplasm and subsequently forms new protoplasm.

Second, when one assumes that in degeneration the conducting mechanism is destroyed, this carries with it the conception that the isolation apparatus belonging to the conducting mechanism, the myelin sheath, is lost. But a comparatively normal relation was found between the nerve and the lemmoblast elements in the different sensory organs, especially in the Grandry bodies of the duck's bill and tongue. There is unanimity of opinion that the tactile disk represents the farther end of the nerve fiber, that is, of the axis cylinder. The nerve fiber loses its sheath at the point at which it pierces through the connective tissue covering and spreads out as a naked axis cylinder to the tactile disk. The neurofibril texture reaches up to the surface of the tactile disk, and, according to Boeke and Heringa, it is connected at this point with the protoplasm of the tactile cell through the peri-terminal net. In the tactile disk, therefore, there is the naked axis cylinder without other elements. At this point, therefore, the degeneration process should be more simply and readily observed.

However, when the nerve fibers of the Grandry bodies are sectioned, the tactile disk, the extension of a naked axis cylinder, does not disappear, but remains as a distinct structure. It remains as such until complete regeneration takes place. What really is lost is the conductive differentiated mechanism of the nerve disk in the protoplasm, together with the neurofibril texture in the surrounding more richly watery neuroplasm, and the degenerated tactile disk consists only of the neucleated protoplasm until regeneration brings it back to life. Meanwhile, the tactile disk remains faded, due to the unfavorable conditions. Also the ganglion cell itself shows disturbances when a nerve process is cut. The important thing to remember is that it is still present, and that later it shows a new differentiation ability in its protoplasm.

In this connection an observation by Levis is of considerable importance. After cutting the developed neurite of a neuroblast in the embryonic ganglion cells in cultures "in vitro," he found that the peripheral end keeps on growing almost as actively as an uninjured nerve fiber, and that under certain circumstances it may even unite again with the central neurite and make a complete recovery. This would indicate that, even in cultures in vitro, sectioning does not necessarily bring about the breaking up of the separated part.

From these facts it is evident that the sectioned nerve process is not destroyed; it merely undergoes a change. The neurofibril differentiation of the protoplasm, the structure for the definite conduction course of the stimulus, and water-rich neuroplasm are destroyed; the nerve process as such remains, together with the protoplasm of the cells of the sheath, to form the Büngner bands that are so important for regeneration. It is also understandable that the isolation mechanism of the myelin sheath is lost. It is also possible under certain conditions that the sectioned part of the nerve process will not recover but will die. However, after months, or even years, it may find the proper connection to bring about a functional recovery. The statement, therefore, that in secondary degeneration the entire peripheral nerve fiber is destroyed is not correct.

What constitutes the nerve sheath? Is the neurilemma a simple structure, only a tubule, formed by the Schwann cells, which surrounds the axis cylinder? It appears to be a double structure. The Schwann cell, composed of nuclear protoplasm, surrounds the water-rich protoplasm of the axis cylinder process, and is also found at the uninjured nerve fiber between the myelin layers. Over this cell there is formed a stronger membrane, partly perhaps from the neighboring connective tissue, or exclusively as a product of the Schwann cells. Stoer designated this fine membrane as the "outer cover," and considered it a product of the Schwann cells. Cajal was of the opinion that the real neurilemma is a connective tissue structure and surrounds the Schwann cell, which he called the Schwann membrane and which is called by most authors the neurilemma. The neurilemma of the older authors is the Schwann cell, which shows a fine outer border line; more recent investigators consider the neurilemma as the fine membrane surrounding the Schwann cell. Boeke is inclined to accept Cajal's interpretation.

In the question of regeneration it is important that the "outer cover" also remains during degeneration. It surrounds Büngner's band. Boeke limits the name Schwann's sheath to the protoplasmic Schwann cell; he considers the neurilemma the membranous outer cover. The two factors are to be kept in mind, as they are important in the question of regeneration.

3. *The Regeneration of Fibers.*—There is still considerable discussion on this subject. Many investigators disagree with Cajal that nerve regeneration, even in the first stages, is free and independent of other tissue structure of the cicatrix. Boeke cannot accept Cajal's assumption that the thin, sharply limited black lines that he observed between the loosely formed connective tissue elements represent the freely growing nerve fiber. In the first place, it is to be remembered that in a neurofibril preparation only a definite element is observed, a differentiation of the protoplasm and nothing more. Care is required not to be led astray in thinking that the neurofibrils are the only constituents of the nerve fibers, as one is apt to do in observing the neurofibrillar structure that dominates the histologic picture when the fixation was not entirely faultless and the proper protoplasmic counterstain was lacking, and when the nerve fibers appear as only black streaks in the preparation. It must be remembered that the neurofibrils are embedded in living substance. The investigator can convince himself of this when studying faultlessly fixed preparations or specimens properly fixed in gold chloride after Bielschowsky's stain. Cajal described the nerve fibers as black streaks floating in space between the connective tissue cells; it can be said that this is not proved, since the fine black streaks represent only the neurofibril strands, only one constituent of the nerve fiber, and therefore either the nerve fibers are so

shrunken that the outer delicate protoplasmic cover has disappeared, or this protoplasmic wall layer was overlooked in the preparation. It is possible that the outer protoplasmic connections were not stained. One need only compare a section stained by the plain Bielschowsky method with one stained by the Bielschowsky method and counterstained with gold chloride; it is surprising to note in the latter how the delicate protoplasmic strands, of which one had no conception before, become evident.

The better the specimen is prepared and handled, the better can one observe everywhere the protoplasmic coating about the black streaks around the neurofibril differentiation. When care is taken in examining preparations and tissues that have been carefully prepared, one can see the protoplasmic relation, also the apparent free and coursing fibers. It is true that there are sections in which the plasmatic cover cannot be seen, but it would be wrong to conclude from this that it is not present.

Then again it must be remembered that in the regeneration picture, in contrast to cultures in vitro or cultures growing in gelatin, in blood, etc., one is dealing with a living tissue, even when the nerves have been sectioned or compressed.

That nerve fibers (for example, in the cultures in vitro) may grow independently is well known. Braus and Harrison's experiments have demonstrated this. Nerve processes may also at times grow freely in the living body, for example, in blood coagulum (Harrison), and in the central canal of the cord (Cajal).

More recent investigations with cultures in vitro by Levi, Mossa and Esaki have shown also that in the outgrowths in tissue cultures a real netlike fusion of the offshoots of the different ganglion cells takes place, and the experiments of Lawrentjew and Grigorieff have shown that if myoblasts are present near the particles of the nerve tissue in the cultures in vitro, the growing nerve processes will at once enter the protoplasm of the myoblast and form there real end-rings and end-nets.

After a nerve is sectioned there begins at once a proliferation, not only of the axis cylinder but also of the Schwann cells and of the connective tissue, and a real conducting tissue is formed. It is well to bear in mind the double nature of Schwann's sheath. The neurilemma is partly destroyed; it shows necrotic changes, manifestations of proliferation, etc., and under certain circumstances may lead to the formation of Perroncito's spirals. But the Schwann cell itself likewise begins to proliferate rapidly, like the axis cylinder. Who, then, will say that it is only the axis cylinder that grows out amid the surrounding living tissue? It is and always remains embedded in living tissue, either of mesodermal origin, as connective tissue, or of nervous origin, as Büngner's bands which develop in the peripheral part of the sectioned nerve. According to Edinger, Henriksen and Spielmeyer, the proliferated Schwann cells form even in the cicatricial tissue of the central stump a conducting tissue, in which regenerated nerve fibers proceed to grow. According to Cajal's original description, the central nerve fibers grow out independently from within the cicatricial tissue up to the peripheral end of the sectioned nerve. At the peripheral part, the Schwann cells (sheaths) of the degenerated nerve fibers change into a peripheral fibrous zone, a protoplasmic axis (the Büngner band) and a clear lymphatic-like, space, which lies between the fibrous cover and the protoplasmic axis. The newly formed fibers are always found, even according to Cajal, in the outer zone of the protoplasmic axis, never in the aforementioned vaginal space. The new thin fibers can always be observed to lie within the protoplasm of the cell strands, and it can be seen that Büngner's bands, which here function as a true conducting tissue, become extraordinarily water-rich and vacuolated, so that the neurofibril strands give the appearance of lying outside the protoplasm, while, as a matter of fact, they always lie within the protoplasm, whether it be the ectodermal Büngner bands or the mesodermal connective tissue elements, as Heringa has shown to be the case for the fine sensory nerve branches at the periphery.

Büngner's bands also restore the connection between the regenerated nerve fibers and the end-organs. The Schwann cells never form "open tubes" at the

end, as has been claimed by Tello and Cajal. Either the vacuolated Büngner bands become smaller and more delicate, extending gradually to the place where the fine lines of the tubular wall become invisible and the tactile cell or the sarcolemma reaches a muscle fiber, in which the fine borderlines pass over, or it is found that the end of the Büngner bands are protoplasmic and finely granulated and in this manner connect with the end-organ. Boeke even observed protoplasmic offshoots growing out from the vacuolated Büngner bands (photomicrographs were demonstrated) and coming in contact with the end-organs. It is also found, wherever a collateral is given off at the end-area from a nerve fiber during regeneration, that it is always surrounded by an offshoot of Schwann's sheath. One never finds a collateral that simply breaks through the wall of Schwann's sheath without bringing about some changes in the wall.

Whenever conditions are favorable, it is always found that the regenerated nerve fibers lie within protoplasm in conducting tissue or in its sheaths, and at the beginning of regeneration a proliferation of this conducting tissue takes place, whereby the conductive function may become intensified. This brings about harmony between the different tissues, the different elements working harmoniously toward restoring a normal relation.

Regarding the composition of the conducting tissue, Boeke states that, as far as can be observed, not only the cells of Schwann's sheath but also the cells of the connective tissue function as conducting tissue; they receive the nerve fibers and are capable of leading them further on.

The results obtained by newer investigations, the differentiation of the embryonal cells under the influence of the "organizers," the study of the periterminal net, the syncytial cell association in the organism and especially the harmonious relation between the different elements of the body and the insufficiency of the old cell theory, as well as the study of regeneration of the sensory end-organs, lead to a different conception of the subject. The formation of the periterminal net, its gradual transformation into a conducting neurofibrillar structure, the regeneration, especially of the sensory organs, can be explained only on the assumption of a differentiation in loco of the conducting substance, that is, from those which usually are missed in the preparation and which Cajal assumed to be the entire nerve fiber. In secondary degeneration the entire nerve fiber is not destroyed; only the conducting mechanism disappears; for example, in the Grandry bodies the nervous tactile disk remains. This contradicts the idea that a new regenerated nerve fiber "grew into" the tactile disk, which itself represents the axoplasm of the nerve fiber. This would indicate that there is a gradual differentiation "in loco" of definite elements that are present.

The old conception of freely growing-out nerve fibers is untenable in a syncytial association of living protoplasm. Degeneration, and especially regenerative new formation, of the nerve fibers and end-organs cannot depend on the activity of a single tissue element of the neurofibril; it is the result of a harmonious combined activity of all tissue elements, the nerve fibers, their sheaths, the connective tissue and the muscle fibers, until the entire organ, muscle fiber and the conveying nerve fiber of the entire muscle again develop a harmonious whole, and the organism again possesses its former equilibrium. None of the tissue elements remains passive; none predominates in its activity. During the regeneration of motor nerves there is proliferation of the Schwann sheaths; this forms the Büngner bands, which grow actively, develop lateral shoots and form new paths and new connections with the muscle fibers that are appropriated by the differentiated nerve fibers. There is a proliferation of the cells of the sheaths attached to the interstitial connective tissue of the muscles, and this is formed into a typical conducting tissue, which represents a general conducting path for the finer nerve fibers. It therefore represents a progressive differentiation of the conductive substance "in loco," always preceded, however, by the already existing conducting differentiation. This constantly undergoes changes until even the endings are again rebuilt and become normal. It is understood that the differentiation takes place only in the continuity of the center with the central

conducting tract; this is not because the nerve cell forms the trophic center. It is hard to conceive of a trophic influence in the sense of metabolic currents at such a distance and by means of so fine a nerve fiber as is present in regeneration.

4. *Autogenous Regeneration.*—Braun and Harrison have shown that the embryonal ganglion cells in vitro supplied with a club-shaped growth, are capable of independent growth. Burrows and Ingebrigtsen have shown that these neurites contain neurofibrils, and that after sectioning the peripheral part degenerates in a typical fashion. This establishes autogenous regeneration on a solid anatomic basis. Levi and Mossa have shown lately not only that the neurites that develop from the ganglion cell in vitro anastomose among themselves and are capable of forming a true net-formed plexus, but also that the neurite severed from its ganglion cell, after a short resting period, again shows ameboid movements, and that the sectioned neurite grows independently, and when it reaches and makes contact with the central end or with another fiber a restoration of continuity takes place. Also, when ameboid movements of the end of the peripheral stump have ceased, according to Levi, the union of the two stumps can again take place. There is here, therefore, the proof of the vitality of a severed neurite offshoot and of the ability of independent further growth without connection with a ganglion cell. The same must be true in living tissue.

According to Harrison, in the normal ontogenetic development of nerve tissues, the nerve roots, the sheath elements are developed from the neural crests and are therefore independent of the outgrowth of the ventral nerve roots. Removal of the neural crests in young larvae of Rana will permit the growth of nerve fibers, but Schwann's sheath fails to develop. Stone found the same to be true in salamander larvae. In itself this cannot be said to be direct evidence of the independent ectodermal nature of the sheath elements. Spemann, Vogt and Woerdeman and others have shown that certain cells may be stimulated to a definite differentiation through an indirect influence exerted by other cells. It appears, however, that Raven succeeded in transplanting the neural crest of the salamander larva into the triton at a point where the neural crest was removed. This transplanted neural crest developed typical Schwann cells around the growing nerve fibers, but the form, structure, etc., of the nuclei of these cells resembled those of the salamander cells. This unmistakably indicated that the development of nerve fibers comes from two different elements.

However, this is unimportant as far as it relates to the aforementioned conception of nerve regeneration. The newer studies of cells and of syncytial relations between different cells have shown that also here the different origins of the cells have no striking importance for the syncytial question. In culture experiments, Haan found that foreign cells, wandering cells, join the syncytium. It is also observed that cells may free themselves from a syncytium and may later join it again. The conductive elements, the nerve fibers, can be observed to be in the most intimate relation with the sarcoplasm of mesodermal muscle fibers, with the protoplasm of the epithelial cells, with connective tissue and with different parts of the body.

The mistake of the old cell theory is that it began with the ontogenetic development of the body and drew conclusions regarding regeneration proceedings. This is altogether too simple. The common harmonious activity between the different elements in such matters shows that it cannot begin with cells, but must take account of the whole and of the common harmonious activity of the different elements.

5. *Neurotropism.*—According to the foregoing conception of the regeneration process, is there still room for the idea of neurotropism as conceived by Forsmann and Vanlair and especially as formulated by Cajal? Vanlair was of the opinion that the direction of growth of the nerve fibers follows the line of least resistance. For the manifestation of autogenous regeneration, Bethe considered an attraction between the two nerve stumps. Forsmann's conception was that the elements of the peripheral parts of the nerve give off chemical substances which attract the

outgrowing nerve fibers, similar to the effect of Pfeffer's chemotactic malic acid or the chemical bacterial products that Massart and Bordet investigated. Neurotropism is therefore basically a chemotropism, and the chemotactic substances are formed by the destroyed myelin and the protoplasm of Büngner's bands. According to Cajal, it is only Büngner's bands that form the substance. Not until Büngner's bands are formed can neurotropism make itself felt; but then the entire course of the regenerated fibers, together with all its windings, is also explained by chemotactic activity, by neurotropism, and not only in the area of the cicatrix.

Lugaro and especially Dustin pointed out the danger of such a conception. Dustin discarded the name neurotropism and in its place substituted the conception of "hodogenesis" the "principle of passage distance" of Held, according to which regeneration succeeds only when through the surrounding cells (connective tissue cells of the cicatrix, the Schwann cells of the peripheral section) there is formed an easy passage for the outgrowing fibers, a true conducting tissue. Boeke cannot accept the idea that the regeneration of nerve fibers is merely a passive act, and that it is subject only to an attraction of chemical substances; furthermore, the length of time that regeneration takes does not favor the conception of chemotactic affective substances. Boeke also thinks that the entire irregular course of regenerated fibers cannot be explained by the assumption of chemotactic substances without assuming a different substance for each change taking place. Finally, he points out that with an intraprotoplasmic position of the regenerated nerve fibers, which he attempted to demonstrate, a simple assumption of a chemotactic affective substance cannot explain the harmonious manifestations of regeneration. The manifestation of ontogenetic development could similarly be explained by chemotaxis, but no one would accept it now. When one is convinced of the intraprotoplasmic position of regenerated nerve fibers and recognizes the harmony of the different tissues in the process of regeneration, one cannot accept the conception of neurotropism. To be sure, as soon as the equilibrium in living tissue is destroyed, as is the case in degeneration and regeneration, different forces become effective: attraction forces, electric forces, forces concerned with growth, regulating forces, etc., but it is only by means of an alternating play between the collective forces that the course of the regeneration process is settled. This interplay is more complicated than the simple assumption of chemotaxis; again, it must be remembered that it is the collective forces that come into play in the living organism itself. It will serve better to drop entirely the conception of neurotropism.

MORPHOLOGIC BASIS FOR RESTITUTION IN THE CENTRAL NERVOUS SYSTEM. DR. H. SPATZ, Munich.

Three distinct processes are to be considered in the restitution of central lesions: recovery of damaged but not destroyed elements, regeneration, that is, the new formation of lost structures, and vicarious hypertrophy, that is, enlargement of remaining parts of tissue as a substitute for the lost part. Nothing definite is known regarding recovery. Regeneration, to be sure, also plays a part in the central nervous system, but the problem of restitution, both for the clinician and for the physiologist, apparently is of little importance. Finally, the proof of a compensatory hypertrophy, interesting as it is, has so far brought forth a few limited cases. Foerster's "reorganization," the functional alteration leading to restitution, cannot be explained from a morphologic standpoint. The regeneration manifestations observable by the morphologist are of no importance to the physiologist, and where the physiologist and the clinician can establish functional restitution, the present methods of morphology can disclose no corresponding changes in the tissue.

Spatz discusses the subject first from the standpoint of so-called "pathologic" regeneration in the central nervous system, the regeneration phenomena as they are observed in experiments and pathologic defects. Then he discusses so-called "physiologic" regeneration, the manifestations during physiologic wear and tear:

then the manifestations of recovery of damaged but not destroyed neurons, and finally compensatory hypertrophy.

The less differentiated a type of cell, the less is it limited in its division and and in its power of regeneration. Conversely, the more a type of cell has developed into definite structures, the more highly differentiated the cell is, the more it loses the power for division and regeneration.

The readily differentiated elements of the connective tissue are capable of wandering in different directions. In tissue cultures they show an apparently unlimited power of division. In the organism the regeneration activity is present even in very old age. The short life of the individual cell means prompt replacement by another. Multiplication and death go hand in hand. The specific supportive tissue of the central nervous system, the glia, as it is now known, is likewise capable of division and replacement, although not to the degree of the mesodermal connective tissue. The power of regeneration of the glia plays an important part in repairing defects, but it has no influence on restoring function.

On the other hand, the parenchyma of the nerve tissue (the central organs) is a highly differentiated type of tissue. The neurons, which in higher vertebrates first acquire the peculiar complicated differentiation some time after birth, in comparison with the young connective tissue cells, appear fixed, unchangeable and more or less sterile. The parenchyma of the nervous system can therefore possess only slight regenerative power.

The process of regeneration is intimately connected with the process of development. B. Dürken designated regeneration as a direct "secondary process of development." In the earlier stages of development all types of cells are as yet more or less undifferentiated and therefore endowed with different potentialities. The power of regeneration generally diminishes with the increased level of organization of the animal series and with the course of individual development. Also as regards the central nervous organs, those of a lower grade of development (phylogenetic and ontogenetic) therefore always possess a better prospect for regeneration.

To begin with the embryo of lower vertebrates, defects in the amphibian embryo right themselves by the so-called road of "regulation." The organ reacts more or less as a unit. The defects originally may have been produced by a different kind of material. Tissues transplanted to different locations develop at the defect ("Ortsgemass"), that is, according to that location. A tissue that should develop into a surface skin can thus develop into a corresponding piece of brain. Different parts of the neural tube can be exchanged among themselves and will develop "Ortsgemass." On the other hand, after complete determination has set in, "individual differentiation" takes place; that is, the substituted or exchanged pieces of tissues cannot be influenced by the surrounding regulation, but develop within the defect according to their origin, that is, corresponding to the original type. The regulation has then more or less ceased. It appears that from that moment on the regulation becomes separated from the real regeneration. Although both processes are closely connected, they must be conceived differently. The manifestation of regeneration in a true sense, that is, the replacement of the area of the lesion of tissue structures once present, apparently first sets in after complete determination. Walter Vogt thus recently observed that the resected caudal part of the amphibian embryo regenerates in its original form at a somewhat later stage of development.

In human pathology, regeneration comes in for consideration mainly in explaining malformations, as, for example, the doubling of embryos, or after early embryonal damage. Apparently the influence of the nervous system on the regeneration of the extremities is closely associated with the manifestation of regulation. Goldstein recently compared the regulation ability of young amphibian embryos with the functional alteration, the reorganization, in central defects in adult man. But this comparison is only approximate, for in man the functional reorganization does not bring about a corresponding change of the substances as is the case in the amphibian embryo.

A complete regeneration of feebly developed parts of the central organs was observed in the larva and also in fully developed amphibia. Caporaso, in 1889, showed that after removing a piece of the cord in a fully developed salamander a new formation of the organ grows out from the remaining stump. More recent works have shown this to be true of the cord of other lower vertebrates. The starting point of the new growth begins in small indifferent elements directly under the ependyma in the matrix, especially the so-called "mantle zone." These cells increase by mitosis and then differentiate and follow the normal development in ontogenesis; they develop into neuroblasts and finally into nerve cells with nerve fibers. It is to be noted that such a mantle zone directly under the ependyma remains permanent only in the lower vertebrates.

The formation of new nerve cells has not been observed in mammals after birth. Here there is not present an indifferent reserve of cells from which ganglion cells can differentiate. All statements by older investigators regarding mitosis in ganglion cells must be viewed with skepticism, since it is possible that they may have been glia cells. Only in the nerve cells of the retina has mitosis been definitely established.

In mammals, therefore, there is no more a question of regeneration, since the neuron as a whole cannot be replaced. The question whether a part of the neuron, such as the nerve process, can be replaced, is in principle to be answered in the affirmative, namely, as regards the peripheral nerves. However, it still remains a debated question how much regeneration of central nerve fibers is possible, i. e., regeneration of a part of a nerve fiber that does not possess Schwann cells but only glia as a conducting tissue.

Long ago, Dentan, Brown-Séquard, Eichhorst and Naunyn, after sectioning the cord in higher vertebrates, believed that they observed a return of union of the tracts and a reestablishment of conduction. This could not be substantiated by later investigations. Although the physiologic observations in themselves were correct, the investigators cited were wrong in their interpretation. Eichhorst and Naunyn regarded the recovery of voluntary movement of the posterior extremities of dogs after section of the cord as an indication of true regeneration. The fact is that it was only reflex motion. Spatz observed the automatic ability of the corresponding organs with isolation of the lumbar cord of the rabbit. Reflex activity develops and is surprisingly complete when the dorsal cord is cut in new-born animals. The flaccid paralysis following the operation in new-born animals is also of a shorter duration than in mature animals after similar operations. When a movement of the anterior extremities is brought about by a stimulus from the brain, the change in position brought about by this movement will also bring about reflex activities in the posterior extremities. This may bring on almost normal movements. The animals move quickly from a position. The impression may easily be gained of a coordination of the extremities. The first impression is that regeneration has taken place; but this is not true; there is no regeneration in the sense of a reestablishment of tissue structures. It is a functional restitution but not a regeneration.

The possibility of a regeneration in the sense of a reunion of stumps of central nerve fibers in mature mammals is unanimously denied. Most experiments were done on the spinal cord, and this applies to either cutting or crushing the cord. In the newly born and in the fetus no better results are obtained.

It must be accepted as a fact that in mammals a reestablishment of conduction does not take place in central lesions. Yet it is experimentally found, after cutting the cord or into the brain, that phenomena are regularly observed in the early stages of the healing of the wound which are very similar to manifestations observed in the regeneration of peripheral nerve fibers. It has been proved definitely that there is an actual formation of new nerve fibers, which grow out from the stumps. Even if these nerve sproutings do not bring about a reestablishment of the old connections, it cannot be denied that a phenomenon is present which at least bears some relation to regeneration. Since Cajal's momentous work, the opinion is generally held that the new formation of central nerve fibers

can be demonstrated only by the neurofibril methods. Cajal described swellings in the nerve fiber stumps which are club-shaped at the free end and which he compared to similarly shaped nerve fibers present during normal development. These swellings may be the starting point for new sprouts, but sprouts may develop from a fiber stump without such swellings. The offshoots are at first very thin and have a tendency to branch. At times they can be followed up to the glia cicatrix, but they seldom pierce through it. More often they form twisted balls. Sooner or later, they break up, most often before the myelin sheath has developed. It therefore is an incomplete, atypical and ephemeral regeneration, or a useless attempt at regeneration. Experiments by Borst, Tello and Oiye showed that in the central nervous system, under favorable conditions, there may develop a new large and permanent growth of myelinated nerve fibers, but a union with the old tracts does not take place.

The question comes up why a reunion of the stumps does not take place in the central fibers, while in the peripheral nerve fibers the same initial phenomena lead to a successful regeneration.

For successful regeneration two factors apparently are necessary. It is important that an activity proceeding from the nerve cell, especially from its remaining process, should find expression in the sprouting, and also that an activity to proceed come from the milieu, that is, from the supporting cells. The central nerve fibers do not lack ability to produce sprouting. This has been proved by many experiments, especially by Harrison, Ingebrigtsen and Giuseppe Levi and his pupils. This, therefore, cannot be considered as the cause of failure of regeneration of the central nerve fibers. The supporting tissue must therefore be held responsible. Yamada has expressed the opinion that, in the cord especially, the fault is with the connective tissue cicatrix. This grows out from the pia, between the two stumps, perpendicular to the axis of the cord, and therefore acts as a mechanical hindrance, while in peripheral nerves the connective tissue proliferation takes place parallel to the axis of the nerve. This hypothesis is not entirely satisfactory. For instance, Cajal has failed to obtain a reunion of the interrupted central nerve fibers even in a pure glia cicatrix. Spatz is in agreement with the majority of investigators that the cause is to be found in an insufficiency of the glia; hence, the regeneration phenomena of the central nerve fibers do not lead to a reunion, and the attempt at regeneration fails to materialize. Even the new offshoots of the peripheral nerve fibers are not entirely successful when they enter glia tissue. This was especially illustrated by D'Abundo in an experiment on young cats. After resecting large parts of the cord, he found a tremendous regeneration activity of the peripheral nerve fibers of the posterior roots. The newly formed fibers, which formed a thick band in the spinal canal, did not unite with the tracts of the two stumps of the cord. Domrich met with the same experience. Observations by Fickler, Lhermitte, Marburg and others in traumatic diseases of the cord in man were similar. They observed that the sproutings or the new offshoots of the damaged posterior roots are capable of entering the glia cicatrix of the cord, but are incapable of joining together.

What causes the deficiency of the glia is hard to say. Cajal, Tello and Rossi think that there is a difference in "neurotropism," in the development of stimulating substances. Dustin and Bielschowsky have expressed the opinion that the directing structures of the band fibers in the distal stumps of the peripheral nerves to a certain extent open the tracts and mechanically point the way (hodogenesis) to the new offshoots, while the glia meshwork, although it is a good medium for the growth of the sprouts, is not capable of giving any orientation in a definite direction. This theory follows the old conception of cells, that they develop more or less independently, and that in regeneration also they are dependent one on the other only in a mechanical sense. On the other hand, modern conceptions stress the intimate relations between the cell groups in their growth as well as in regeneration. Here is to be mentioned Spielmeyer's conception of axoblastic activity of the Schwann cells in the differentiation of the conductive elements in loco. Boeke expressed a similar opinion. In regeneration, according to Spiel-

meyer, the Schwann cells appear to be supplied with "greater building potencies" than the one-sided differentiated glia cell. But these differences between the Schwann cells and the glia are none the less astonishing. Spatz admits that fundamentally this question as to why the glia fails in nerve fiber regeneration has as yet not been satisfactorily solved.

So far, what has been said relates exclusively to results obtained in animal experiments. Pathology has taught that in man, after birth, a new formation of nerve cells does not take place, just as in mammals (with the exception, perhaps, of certain cases of ganglioneuromas). Also, in man a reunion of sectioned central nerve fibers is impossible. It is another question whether after compression of the white substance, without a break in the continuity, the conductivity cannot be reestablished. Observations by Fickler and O. Foerster make this appear to be possible.

The phenomena of the sprouting of central nerve fibers in man have repeatedly been observed under a variety of pathologic conditions. Most of the investigations were made by the neurofibril method, and at times too great an importance was probably assigned to the proof of an end-formation. Nerve fibers with end-formations, branching and atypical in course, are found near softenings, at the edge of tumors and granulations, in multiple sclerosis, in tabes, in gunshot wounds and on the border of the so-called senile "glands." The newly formed nerve fibers are present in large numbers, especially near blood vessels.

The difficulty with all these observations is the inability to distinguish between the newly formed fibers and old ones. End-formations are no indication that the formation of new fibers, of new sprouting, has taken place. It is known that swelling of the ends, formation of rings, etc., may take place with no sign of new formation. It is also known that these phenomena are not essential for bringing about sprouting. In regeneration of the peripheral nerves, the end-formation disappears when reunion of the stumps takes place without hindrance, with the influence of which there is perhaps some relation. Spatz thinks that these phenomena are often observed, but are not necessarily the accompanying symptoms of sprouting.

So far the observations on human material are based on the results of Cajal's experiments. The question must be raised whether there are examples in which the position of the nerve fibers is an evidence of a new formation. So far there is only a single example in human pathology that can be used in this sense and that actually possesses experimental value. B. Pfeifer had the opportunity to study several brains of patients in whom exploratory puncture had been performed at different periods before death. He found that the puncture was quickly closed by supporting tissue. From his description it apparently was composed mainly of protoplasmic glia. In these fine narrow cicatrices there were later found entangled nerve fibers which might have been newly formed.

Experiments by Borst and Oiye have shown that the glia in fine, long channels offer a favorable growing medium for nerve fibers. These sproutings may remain indefinite, and are covered with myelin. They can therefore be observed with a myelin stain. These observations led Spatz to interpret a not unusual pathologic phenomenon, the manifestation of which has received but scant recognition. It consists of a number of small cicatrices, and macroscopically represents a definite picture which Spatz terms "granular atrophy of the brain cortex." It is similar to granular atrophy of the kidney. A disease of the arterioles, such as arteriosclerosis of the small cortical vessels, may be responsible for it. While arteriosclerosis of the larger pial bloodvessels leads to softening and ultimately to the formation of cavities or connective tissue cicatrices, lesions of the small cortical blood vessels bring about glial cicatrices. (Therefore Alzheimer spoke of perivascular gliosis.) Spatz considers them a product of an abundant sprouting of central nerve fibers, the basis of which consists of narrow glia cicatrices, as observed in human cortical conditions in Alzheimer's "atrophic lesions." These small lesions are easily recognized in Nissl preparations. (Spatz presented many photomicrographs to illustrate this condition.) In myelin-stained specimens in

locations where the nerve cells have disappeared, there is an increase in the myelinated nerve fibers. In Weigert preparations they appear as dark spots. These "myelinated spots," as Spatz calls them, are the plaques fibromyéliniques of Cécile Vogt. Formerly they were considered as malformations. Spatz came to the conclusion that these paradoxic phenomena, an increase in the myelinated fibers in an area of complete nerve cell destruction, can be explained only by the assumption that an atypical luxurious regeneration took place from the stumps of the interrupted nerve fibers.

Bielschowsky disagreed with this interpretation of the "myelin spots." Staining by his neurofibril method, he failed to find the end-formations. But since the nerve fibers here already possess a myelin sheath and there are no signs of recent decomposition, it must be assumed that the new formation has been going on for some time; experimentally it is known that the end-swellings are not then necessarily present. Bielschowsky thinks that the myelin spots may be the product of the remaining myelinated fibers, entangled and pressed together by the cicatrix. Spatz is of the opinion that this possibility can be excluded. With greater magnification it can be observed that the fibers in the myelin spots may be more thickly or more loosely arranged, and entangled in all possible directions; they do not look like a compression of normal structures. In addition, the remaining tissues at the margins of the lesions show no distortion. Finally, it is to be noted that the myelin spots are often found in the outer cortical layers, an area that contains but few myelinated fibers. Bielschowsky also suggested another possibility. He thought that it is possible that the nonmyelinated fibers in the lesion remain intact and under pathologic conditions become covered with myelin. There are two objections to this hypothesis: If all other structures are destroyed in the lesion, why should the nonmyelinated fibers survive, and why should they especially here be covered with myelin? Aside from that, there is often a very large increase in fibers with atypical arrangement which can be explained only by an assumption of a new formation.

On the other hand, the assumption that the myelin spots are a product of regeneration accords well with the observations of Borst and Oiye. These fibers are found only where the cicatrix has a purely glial character; they never enter into mesodermal connective tissue. They are myelinated and have an irregular course. They are found in large quantities. It must be assumed, therefore, that overproduction is the cause. In young persons they are more abundant than in old persons; in very old arteriosclerotic persons, myelinated spots are found only sparingly in the cicatrix. This too agrees with general experience in regeneration. Although there is a failure at reunion, the newly formed fibers apparently may remain for a long time. An analogy is found in the amputation neuroma of peripheral nerves, with which the myelin spots may well be compared.

The myelin spots are found in large numbers in granular atrophy of the cerebral cortex. Single ones are also observed occasionally. Oskar and Cécile Vogt even believe that there is scarcely a brain in which the spots cannot be found if careful search is made. Assuming the correctness of the regeneration hypothesis, Spatz argues that the conclusion must be reached that the sprouting property of the central nerve fibers is more intensive than is generally assumed, and that this property also plays a larger part in human pathology than has been suspected.

However, the sprouting does not mean a restitution of function. Regardless of an overproduction of newly formed fibers, the old connection is not reestablished, and yet this fact is perhaps not entirely without some importance to physiology. It is known that there are many activities in life the effect of which cannot today be recognized from a change in structure. At times an anatomic observation is only an accidental equivalent to the forces active during life. Although this abundant sprouting formation of the central nerve fibers, expressing itself in myelin spots, is not a morphologic expression of functional restitution of the central nervous system, Spatz thinks that he is justified in seeing in it an indication of the building-up forces that may lead to restitution of function.

Physiologic regeneration, that is, the ability to renew the wear conditioned by ordinary life, is to be distinguished from so-called pathologic regeneration. Corresponding to the high grade of differentiation of nerve cells, it is generally assumed that soon after birth man depends for the rest of his life on a stable condition of the neurons, a state that can in no way be restored. It appears that this conception is not entirely correct. Agduhr, in very careful studies with exact counting, has shown in cattle, cats and dogs that the number of neurons appreciably increases in the course of intra-uterine life. Therefore, the new formation of nerve cells takes place for some time in postembryonic life. The occasional discovery of double nucleated nerve cells apparently also speaks in the same sense. It is possible that this division takes place by amitosis. But the ability for division of fully developed nerve cells is very limited; this would indicate that this ability practically does not come into consideration in experimental sectioning and in pathologic defects. On the other hand, this possibility of increase should be sufficient for a long time to offer a replacement of early wear and tear. The dogma of complete inflexibility and sterility of mature neurons to a certain extent must be restricted.

A great deal cannot be said on the question of recovery of damaged but not destroyed nerve tissue. The morphologic evidence that regressive change in the nerve parenchyma may be reversible is likely. Here can be mentioned Nissl's acute nerve cell change, which has been compared to cloudy swelling. It occurs in many conditions, especially in acute infections and in intoxications. Spatz failed to find it experimentally. Strict evidence cannot be brought forth that the acute nerve cell change is in principle reversible.

Another example of nerve cell change is that found in old persons. The cell is observed to increase the storing of pigments, which are designated as wear and tear pigments. This is often found in other chronic processes. The pigment is apparently a metabolic sediment which cannot be eliminated as it used to be. In nerve cells, the wear and tear pigments, with astonishing local variations, begin to appear as early as puberty, and become more distinct; in the aged they fill up a good part of the cell. Is this process reversible? Can the altered cells again rejuvenate? Harms, in old dogs, observed trabant glia cells in the neighborhood of ganglion cells; the trabant cells were overfilled with pigments, while the nerve cells contained less pigment than ordinary nerve cells. Harms thinks that the trabant cells, as phagocytes, have taken up the pigments, and thus a regeneration of the ganglion cells is brought about. Spatz, while not accepting entirely the foregoing observations, thinks that it is worth while to follow up Harms' experiments.

Definite progressive changes may be restored to the old condition. This is the case in "primary stimulation." When a nerve process is sectioned or damaged, characteristic Nissl changes appear in the nerve. In primary stimulation it is also spoken of as regeneration because it is known that this change is followed by reestablishment of a normal cell picture. But these changes are perhaps better considered as "recovery," since the process taking place in the cell body is not necessarily a new formation. On the other hand, the process has undoubtedly a progressive character. The swollen cell body is filled with plastosomes, and changes are also observed in the nucleus which are to be considered as progressive.

Aside from the central nervous system, the striated musculature and especially the heart muscles live as long as the entire organism. Here the lack of regeneration ability is replaced by the power of the remaining structural elements to develop a compensatory hypertrophy, so that the activity of the organ will not suffer. This is a morphologic expression. Is there a compensatory hypertrophy in the central nervous system? In principle this can be answered in the affirmative for man. However, the observations are not many, and nearly all relate to young persons. Monakow, Dejerine, Pierre Marie and Guillain have described an enlargement of one pyramid when the other pyramidal tract was lost. Haenel observed hypertrophy of the rubrospinal and tactospinal bundles in atrophy of the pedunculi cerebri. Similar observations were made by Anton in the cerebellum in a case of aphasia. In a case of atrophy of the cerebellum, Spielmeyer observed enlargement

of individual Purkinje cells, and considered this as a compensatory hypertrophy. In this case also the damage must have taken place early in life. Nissl and Cajal have made similar observations.

In summing up, it can be said that observations on compensatory hypertrophy indicate what intimate functional relations there are with the lost systems: (1) in the damaged neuron itself; (2) in single neurons in the neighborhood of destroyed nerve cells, and (3) in the entire neuron system. It is not to be doubted that the morphologically recognizable increase in volume is to be considered as an increase in activity, and that this increase in activity means a replacement of activity disturbance. But can an increase in activity find its expression only in hypertrophy of the substrate? This cannot be assumed a priori. At present there is no means of studying the elements during life. The morphologist observes only the negative, the regressive changes and the loss of substance. The positive side of the substrate can be observed but little.

Attempts at newer methods of study have begun. The discovery of a physiologic storing up of iron, which reaches regularly a definite proportion in different brain centers, permits the thought that this may have some relation to function. Oxidation processes have so far led to no results. Marinesco found, after sectioning of the cord, a strongly positive oxydase reaction in the nerve fibers of that area. He also observed a large number of oxydase nuclei in the glia cicatrix in which young sprouts grew, while in the connective tissue cicatrix where the sprouts do not enter he observed very few granules. These studies are mentioned to show the attempts that are being made to bridge over the gap that exists at present between what is observable in the substrate and the changes that undoubtedly take place during functional activity.

The gap becomes more evident when one compares the anatomic material reported with the facts of physiologic restitution. The functional changes that take place in the isolated lumbar cord of the experimental dog continue without any objective changes in the structure; that is, the nerve cells of the lumbar cord appear to be no different during the phase of automatic function of the posterior extremities than during the preceding phase of flaccid paralysis. The cells do not appear to be different from what they were before the lesion was brought on. When, after a brain lesion, the function of the lost part is apparently taken over by other parts, the remaining organ shows no recognizable structural changes, excluding the occasional cases of vicarious hypertrophy. In a mature amphibian in which, after implantation of a new extremity, the innervation was for two legs instead of one, Paul Weiss could find no histologic change from the normal. Bethe met with a similar experience. These facts force one to the conclusion that a study of the structure with present-day means does not form a sufficient basis for explaining the course of nerve function.

FUNCTIONAL REPRESENTATION IN THE CENTRAL NERVOUS SYSTEM IN EXPERIMENTAL INTERFERENCE WITH THE ORGANISM. DR. R. MATTHAEI, Tübingen.

The conception of restitution is based on the assumption that a defect is brought about as the result of a lesion, and that this defect can again be righted secondarily by means of complete restoration (regeneration) of the destroyed part, through activities replaced by other parts or through the disappearance of accompanying manifestations of the damage. The defect is considered as a loss of certain functions which anatomically are considered centers. Bethe, Goldstein and von Weizsäcker are against such a conception; they take into account the entire organism. The lesion not only destroys a part of the organ, but, much more, injures the entire central nervous system, and this reacts at once to the changed situation. Experimental investigations are no longer divided merely into stages of defect and restitution, but are described as a process of the whole.

W. R. Hess recently pointed out that there are two ways of experimental investigation of the function of the central nervous system, the "descending," which primarily injures the center, and the "ascending," which begins with an injury

to the periphery. The descending method is more appropriately studied by the morphologic anatomic investigation. The ascending route leads to the investigation of all the systems; it is based on the conception of ordination laws that are of a more dynamic physiologic type. This line of investigation holds before it the unity of the whole nervous system. In peripheral injuries the entire organism is affected. Goldstein stated that every change in the organism brought about by stimulation affects the entire organism and expresses itself in a change in all the organs.

W. Trendelenburg performed the following experiment: The left area of the cortex supplying the arm and leg was cut off flat in the baboon. The sulci remained uninjured at the base. In eating, the animal used the left hand. After seven weeks the left arm was amputated. The animal then attempted to use the right hand. On the next day, there was considerable improvement in the use of the hand. On the ninth day, the use of the hand had reached almost a normal state. The sulci in the area operated on were then cut away deeper, whereon the animal lost the power of grasping with the remaining hand. However, grasping was again developed when the food was placed outside instead of inside the cage. Even then, however, the grasp remained awkward and clumsy, and there was a loss of the finer movements of the fingers. Electric stimulation over the right cortex brought no response in the right arm and hand.

A partial lesion of the motor area brings about a complete loss of function of the affected extremity. However, the function shortly returns if the opposite normal extremity is amputated. A further injury to the cortex weakens the motility of the damaged arm. Therefore the effect of a central lesion depends considerably on the condition of the periphery, and even on the entire situation of the animal.

These observations lead to the thought of an objective function. When the right arm of the monkey is damaged, the left one is used; when this arm is removed, the right damaged arm is again called on to function. If the damage is increased, the animal makes use of the teeth to grasp food. If the desired object, food, lies outside the reach of the head, the badly damaged arm can again be made useful. The organism defends itself against danger; it attempts to perform the important functions of life with the means remaining at its disposal.

The conception of an objective aiming becomes especially evident when different objective movements take place which, between themselves, are in competition. When one is tickled on the head, a scratch movement with the homolateral hand usually follows; if this hand is at the time engaged in another way, the opposite hand may be used if the itching is strong. Other similar observations can be made. It seems, therefore, that the objective aiming is not related to the repair of the central nervous system.

Three types of peripheral attacks are to be considered. One may consist of a simple moderate change in the situation (stimuli constellation). Resections may be undertaken. Finally implantation of surplus limbs may be tried, care being taken in the ingrowth of the nerves.

Amputation experiments on anthropods offer especially favorable results. V. Buddenbrock studied the coordination gait of the grasshopper (Dixippus morosus). In walking, these animals show a crossing; the left foreleg, the right middle leg and the left hind leg are put forward simultaneously, while the animal is standing on the other three legs. If both middle legs are amputated, the right hind leg assumes partnership with the left fore leg, and the left hind leg works together with the right fore leg, whereby the partners do not move simultaneously, but one moves somewhat after the other. For this new coordination apparently two changes were necessary. Such changes become especially numerous when only one leg of the normal series remains. In appropriate amputations, adjacent legs may become partners, an adjustment that never takes place in the normal animal. Even more numerous are the readjustments in animals with many legs. Bethe carried on similar experiments on the shepherd spider (Opiliones). The crossing type is also found here, and the coordination adjustments are especially numerous,

reaching 255. In animals possessing the ability of self-amputation, one would derive the idea that the readjustment after the loss of a leg was in some way already preconstructed in the central parts, especially as it appears immediately after the injury. But in the face of such a large number of readjustments, such an assumption is unreasonable. The facts rather call for a correction of the conception of a rigid center. Bethe therefore spoke of a flowing distribution, and assigned a plasticity to the central nervous system.

The type of gait in the different injuries is found to be always the same. In all cases a crossing takes place, in the shepherd spider as well as in the grasshopper. The numerous readjustments are not as remarkable as the fact that they always result in the same type of gait. This may be called a regulated motility.

Goldstein and Gelb described a case of complete destruction of one visual field, in which the hemianopia was to be found only perimetrically; in ordinary vision the patient saw the entire field, but the picture appeared smaller. Goldstein stated that the motive for the change is apparently the necessity that the organism have a visual field according to normal structure. As stated by the formulators of the Gestalt theory, the principle of retaining a "stimulation form" holds true for the processes of the central nervous system. This principle is observed in the shepherd spider; no readjustment follows when the remaining four legs are left in the normal partnership. More recent investigations of the case reported by Goldstein and Gelb indicate that it apparently depends on this principle: The characteristic constellation of developed stimuli comes from the periphery. The position of the eyes is so changed that the object does not fall on the macula, which now would lie on the border of the visual field, but rather on a part that is surrounded by active visual retina. The presumption is that the sensory stimuli coming from the moving extremities are of considerable importance. In the center of the constricted visual field there is a new place for clear vision. The same stimuli Gestalt is also attained here, but with different accompaniments. In the Gestalt theory, one speaks of transposition ability.

The possibility that the coordination changes as observed in the experiments described are due to stimulation from superordinated centers can be entirely excluded. V. Buddenbrock thought that the displacement of the center of gravity in the gait itself could be the inciter for the stimulus. But an ingenious experiment disproved it. He replaced the removed middle legs by artificial ones, so that the stumps of the middle legs could touch the surface of the artificial legs. No rearrangements then took place, the stumps of the legs moved in a normal gait, and the animal walked on its four end-legs. According to this observation the leg stumps apparently move correctly only when, to a certain extent, an effect of the movement is well founded for the animal.

Matthaei reached the conclusion that definitely matured afferent stimuli not only hinder the permutation, but condition entirely different reactions. Bethe found that the effect of fettering an extremity is not the same as that of amputation. A dog may run well on three legs. If a leg in a flexed position is put into a cast, the animal is greatly hindered, and is incapable of normal walking. After the posterior roots appertaining to that leg are sectioned, the animal can run dexterously on three legs. Apparently the proprioceptive stimuli disturb the normal readjustments of coordination. This experiment finds an interesting analogy in experiences gained in brain injuries, that patients with complete destruction of a part supplying a definite function often are less affected than those with a partial lesion. Goldstein compared this with the observation that in partial calcarine injuries the visual disturbance is marked, while in complete unilateral destruction there is merely a constriction of the entire visual field. This would seem to substantiate the principle of the presence of a stimulus Gestalt. It becomes intelligible when peripheral experiments are made; the organism is then in a state of defense against a partial injury. Matthaei pasted the thigh of the left middle leg of a beetle to the body, and amputated the right middle leg. Proper locomotion did not take place; the left hind leg was always kept under the body. Apparently the attempt to free the leg prevented the readjustment. On the other hand, total amputation forced the animal into readjustment.

The gradual removal of perceptible objects, such as optic figures, brings about to a certain extent the destruction of the original object presented. But with complex figures it is often observed that in a systematic progressive removal, figures again appear that are similar to the one that has disappeared. This rule is a proof of the law of degrees in the theory of form ("Gestaltlehre"). The removal of perceptible objects is not a continuous one, but is steplike. In a changed relationship in which a considerable reduction of power is brought about, a principle enters that aims toward reaching a definite object. Goldstein spoke of a "roundabout way of service." The animal may thus acquire new types of locomotion. The two-legged spider that also has lost the feeling legs of the jaw puts both legs simultaneously sideways.

In other cases only parts of the body show new function. Thus the two-legged spider makes use of the jaw feelers in walking. Again, a tendency toward maintaining the motility type can be observed. Similar observations were made by Bethe on the turning reflex. This can be stated to be the rule: The motion form (Bewegungsgestalt) that the animal produces normally with definite organs can be brought about with other organs after injury. The central nervous system as a unit possesses to a certain extent the ability of performing those definite movements, and is therefore in a position, in case of necessity, to perform the same by abnormal means (transposition ability). In agreement with this is the observable fact that a "stimulus form" to one part may be utilized by the entire central nervous system.

For the problem of restitution there remains to be answered the question of how the supernumerary extremities reach the proper stimuli over foreign tracts. Anatomically, it is entirely unintelligible, when it is considered that nearly all the implanted muscles are connected with central parts supplying other muscles and at times even antagonistic muscles. An explanation is possible only under the assumption that a definite central impulse passes over all nerve tracts, at least over a large area up to the organs of reaction, and that, on the other hand, an afferent stimulus reaches all the central parts of the area. A definite reaction can then be understood to be developed only by the assistance of qualitative moments. There follows the important consequence that on the same tract a variety of play may take place, and that the determining results (at least as far as motility is concerned) lie with the organs of reaction.

In this connection it is well to recall the observations of Adrian and Bronk. By diverting a few fibers of the phrenic nerve in rabbits, they found an action current frequency of from 20 to 30 per second in quiet breathing; in dyspnea the frequency increased to from 50 to 80, and once it reached 112, while the amplitude remained unchanged. Similar observations were noted in the motor nerve fibers of the skeletal muscle of the cat.

Instead of a differentiation between defect and restitution, investigation has offered a unified proceeding, in that the organism reacts in a defensive sense to all dangers in which it finds itself. The intimacy of a close relationship of function permits the assumption of the law of order under which in experimental injuries of the periphery, the function Gestalt takes place in the central nervous system.

The manner of the reactions of the organism is under the guidance of a changeable order which follows the principle of maintaining a transposable stimulus Gestalt. The minimal condition for maintaining this principle is given by a graded law conformable to the gradual disappearance of the form—Gestalt—measured by the organism. A higher limit is found in more extensive injuries, and is changed as a result of the principle of the newer relation toward attaining a vital goal.

In the latter principle the close relationship of the adaptability of function is also recognizable. The entire nervous system partakes in the formation of a stimulus form ("Erregungsgestalt"). Different qualitative stimuli may pass over the same nerve tract, and the regulated activity of the central nervous system can be explained only on the basis of the assistance of a qualitative moment of the individual stimuli.

(To be continued)

LOS ANGELES SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, March 25, 1931

I. LEON MEYERS, M.D., *President, in the Chair*

PSYCHIATRIC POINTS OF VIEW ON CHILDREN'S PROBLEMS. DR. FORREST N. ANDERSON.

The psychiatric study of children represents a comparatively new development in the modern attempt to keep abreast of the increasing complexities of an urban civilization. It involves the coordinate application of the technics of a minimum of four professional fields—psychiatric social work, psychology, general medicine and neuropsychiatry. It is this broad use of the term, as including many facts and methods not belonging to the psychiatrist as such, that is meant when one uses the expression "psychiatric." I can only very briefly set forth the skeleton framework of the application of this idea.

Problems that can be grouped under the general headings of conduct, habit and personality constitute the sphere of operations of child psychiatry. In the main, only children of average or superior intelligence are effectually dealt with. The parent, school, physician or agency having control or contact with a child presenting such a problem refers the case. The psychiatric social worker obtains a history of the situation, replete especially with matters of relationship and attitude between child and parent, parent and parent, child and siblings, etc. Then follows the objective study of the child himself by means of physical, neurologic, psychologic and psychiatric examinations. Following all this, a composite interpretation is evolved and a long time plan of treatment commenced.

Grouping these various approaches together one may say that the basic idea is that of the existence of the cause-effect relationship in behavior. The mere fact of behavior presupposes a cause, and that cause is almost invariably multiple. Furthermore, the operations of these causes are usually below the level of consciousness. The realization of this fact alone constituted a tremendous advance and laid the basis for most of the modern points of view on behavior. So long as conduct was a matter of knowledge it was bound to remain largely a matter of good and evil. When it became a matter of emotion it was no longer so clear, and it might be possible for the individual to be not quite as morally responsible as had been supposed. In other words, behavior ceased to be fundamentally a matter of morals and became an exploratory field of science. It is no longer believed that the patient's assignment of a reason necessarily means anything approaching the fact; nor is it believed that his "I don't know" represents mere stubbornness. As a matter of fact, what he says in this connection is all too often literally true.

The main purpose aimed at is an understanding of the child. If this is what is meant by diagnosis I believe in diagnosis. A child of certain stature physically, intellectually, emotionally and socially is presented as in trouble. The present situation is a cross-section of life, for the evaluation of which a longitudinal section is indispensable. The influences of heredity and family relationship combine to produce the personality, a personality that is soon affected by countless other relationships of school, play, work and church. Presently, there develops what may be referred to as a "self-motivated" person. By this it is meant that he has incorporated within himself many of the originally outside demands of parents and of society generally. He may then be said to have internalized his environment. Such internalization is essentially unconscious, and when it has occurred in any particular field of the person's activity, manipulation of the environment is of relatively slight value. This state of affairs is encountered frequently. The process occurs whether the resulting personality is normal, antisocial or psychoneurotic. It leaves a conviction that more and more intensive work must be done

with the individual person—that he must in some way be led understandingly to experience the nature of his own drives, and by this combined intellectual and emotional insight in some degree to redirect his energies into socially acceptable and individually satisfying directions. As a large share of the internalizing stimuli comes from the parents in earlier life, much effort is directed toward alteration of parental attitudes, striving slowly to help them to experiential understanding of their own motives and impulses, to the end that the actual environment of the child may be altered for the better. For there is reason to believe increasingly that it is the emotional environment of the child that is the most important stimulus to the development of his character and behavior.

I repeat that one recognizes in the activities of the child the responses to a multiplicity of stimuli—physical, chemical, nervous and emotional. I do not believe that these can be, or in fact should be, separated in study and treatment. However, the greater tangibility of physical factors, as well as the possibly greater knowledge concerning this group of factors, is recognized. At any rate, the physical equipment can be more generally estimated and appropriate action often taken. This is believed to be the only sound point of view to take. Moreover, since the nervous and endocrine systems represent the primary coordinating systems of the body, I believe that especial attention should be given to them.

I have tried to show thus sketchily that the most fundamental aim in child psychiatry is this uncovering of causal relationships; this is in harmony with other fields of scientific endeavor. The accomplishment is probably in part on this basis and in part on a less demonstrable one, i. e., what may be called the arts of the combined fields of social work, psychology and psychiatry.

In passing, it may be said that much can be accomplished by an attempt to apply broad principles of mental hygiene to specific problem situations. One is surprised repeatedly at the frequency with which what would seem obvious matters have to be dealt with, with little or no appreciation on the part of the parent for the child's impulses, wishes or needs. I refer particularly to such things as the formation of habits and attitudes toward them; to the need for judicious ignoring of irritating behavior, and to constructive recognition of the child's basic needs of security, affection, etc. I have not, however, deemed it possible to enter into any discussion of these.

I wish now to present a summarized report of a case which, stripped of technicalities, shows something of the most frequent and obvious difficulties of attitude, and the need for a comprehensive treatment point of view.

REPORT OF A CASE

A boy, aged 9, was seen with the complaints of nervousness, difficulty in management, enuresis by night and frequent micturition by day, and epistaxis. As the patient developed, he was found also to be "guilty" of stealing, lying, truancy, masturbation, running away from home, cruelty, etc. At school and at home alike his physical restlessness was irritating in the extreme.

Physical examination revealed that he was 12 per cent underweight, and had a rather high arched palate, a functional cardiac murmur and urine of low specific gravity. This was superimposed on a history of his having been a seven months' child.

Psychologic tests showed average intelligence, with unusually good grasp of form and space relationships. The child worked steadily, even in the face of obvious fatigue. Egocentricity was pronounced; this was evidenced even in his definitions of abstract words. Thus, skill meant to him: "If I'd just skin into the next grade, which I don't think I'm going to do."

Then the "culprit" told his story—long, circumstantial and interesting. I can select only the briefest samples here and there to point toward an interpretation as the situation worked out with him and to him. There were much bluster, bluff and self-hypnotism in the recital of his assumed powers, so pathetically out of keeping with the facts: "There's one thing, too, I won't eat, and that's fat meat;

I can't hardly ever look at that; it gives me a shudder. My mother can't either. And I don't drink milk and that's why I don't get fat. . . . And I am nervous, I have been all my life. They just about did get me. I was as sick as the deuce when I was born and they just about lost me." (And what makes you nervous?) "I'm always so twitchy and everything; I'm always teasing somebody and everything." (How did you know you were nervous?) "My mother always said I was and after she said it I had to be—had to act nervous, I mean. Sometimes I am nervous when I don't want to be though. . . ." When enuresis was being discussed he stated that he believed drinking water caused this difficulty. (Yes, but every one drinks water, does he not?) "Sure they do, but others control theirs; they ain't nervous."

Enuresis was discussed in detail with the boy, with emphasis on his responsibility for this and other infantile behavior; he was told that there was nothing "wrong" about these habits, but that they were simply too childish to be continued long in a lad of his capacity; that water restriction was not primary, etc. In general the psychiatric concepts of such habit formations as enuresis were used as a basis of discussion. Attempts were made to mitigate the "inevitableness of the nervous causation" attitude.

In view, however, of his definite physical underparity he was sent to a medical clinic, especially for a study of the chest, kidneys and nose. There he was put on a very strict diet for enuresis; immediate tonsillectomy and adenectomy were advised; the mother was informed in the presence of the patient that it was her responsibility to see that he arose at night. The definiteness of the recommendations carried conviction, and for a few nights dryness resulted; then the inevitable happened and the bed was again wet. He now irked under the rigid routine, and a competitive struggle developed between mother and child.

It should be added that when after some months of varying vicissitudes the boy came again to the clinic, he was found to have systematized his unacceptable behavior into a "bad boy ideal" of himself, striving with such pathetic bravado to impress the examiner with his toughness. When these exploits were met with nonchalance and interpreted as sheer babyishness he was at once put to it to keep from facing his behavior for what it was. As he was confronted with this point of view it was hoped that he would come gradually to find that responsibility means growing up and that growing up is worth while. But the patient remains in a paradoxical position at the time of this report. At the medical clinic, where time is all too brief, he is seen by two or three physicians who stress in varying degrees methods for his physical upbuilding as well as for the control of his enuresis. At the child guidance clinic he is presented with points of view that demand that he assume more of a part in his behavior. He eludes each side and goes on in his disruptive conduct. The medical clinic is handicapped by lack of available time, and (as I see it) by a failure to appreciate the complexity of the problem; the child guidance clinic is handicapped by the lack of a more effective integration of all facilities for treatment.

I have made here several worth while observations, the first of which is the inextricable interrelationship of the physical and the psycho-emotional as determiners of behavior. One might argue all day on the primary importance of one or another of the boy's physical defects. The psychiatrist believes definitely in the importance of these defects, but he does not believe them to be effectively remediable, so far as the behavior difficulties are concerned, apart from consideration of the attitudes developed and engendered. He believes that the boy's own statement as to the congenital nature of his nervousness has all the working force of a fact—although the existence of such a fact is uncertain. Whether the nervousness is inherited, congenital or acquired makes less difference than the attitude toward it. The boy has grown up under the oppressive belief in a nervousness that caused and explained his behavior. For him responsibility was thus avoided, and, as the avenue of least resistance, this attitude was almost certain to continue unless challenged. Then, there are the troubles growing out of an emphasis on one aspect of a problem, whether physical or psycho-emotional. Furthermore,

there are the compensating endeavors of a youngster to function in conformity with some ideal of accomplishment, even if it is that of antisocial accomplishment.

DISCUSSION

DR. ARTHUR TIMME: Dr. Anderson is to be congratulated on a clear and succinct statement of some of the fundamental points of view of modern psychiatry. This is a controversial and contentious field of thought. One may, however, first admit the premise that the human being is a behaving animal. One can then speak of normal and abnormal behavior and of psychoneurotic, psychotic and criminal behavior. The causes of behavior have always been a matter of interest. It was not so long ago that disturbances of behavior, e. g., illness, mental disease, etc., were said to be due to supernatural causes—possession by demons and the like. Scientific medicine brought behavior into close relationship to the structure of the human organism. It was then natural to attempt to explain all deviations of behavior by changes in the anatomy or at least in the physiology of the body. The limited, intensively individualistic training of the physician fosters this point of view.

The present century has brought a new point of view. It is realized not only that there is an organism that behaves, but that this organism behaves in accordance with its experiences. Nowhere is this more clearly shown than in the field of child guidance. In order to understand the child's behavior, one must appreciate the experiences the child is exposed to, in other words, his environment, as well as the attitudes and influences of his parents. These attitudes and the child's reaction to them are determining factors in shaping his present and future behavior. In this interplay are frequently foreshadowed future neurotic, psychotic or criminal behavior.

It is in this early period, when behavior is in the making, so to speak, that much can be accomplished in treatment. Therefore, mental hygiene and child guidance are the contributions that psychiatry has made to preventive medicine. Has not psychiatry thereby kept pace with other branches of medicine? I think it has.

Book Reviews

Problems in Psychopathology. By T. W. Mitchell. Price, $3.50. Pp. 187. New York: Harcourt, Brace & Company, 1927.

In reviewing the history of psychology, Mitchell devotes twenty-four pages to its history before Freud, and 160 pages to its development since. He believes that the effort to raise psychology to the objective level of other sciences has resulted in an overemphasis on the organic or physiologic aspects of the problem, and he calls attention to the fact that it was investigation of such "functional" conditions as hypnotism that opened the door to the understanding of the mind.

The discussion of the freudian hypothesis is opened with the observation that the scorn with which it was received is evidence of its truth; a popular reception would have cast doubt on the validity of psychoanalysis. In his discussion of the libido, the author admits its presexual origin, but insists on a simplified conception of libido as a sexual drive. Between its phylogenetic and ontogenetic development he draws an ingenious parallel. The freudian theory of hysteria and psychasthenia is explained in clearly understandable terms; somewhat more vague is the presentation of dementia praecox as a fixation of the libido onto the ego. Curiously enough, in presenting Freud's idea of the verbalized nature of the preconscious, the author draws support from John B. Watson. In discussing instinct, the author deplores the vagueness of that term and offers to make it more precise by defining an instinct as a "stimulus to the mind." He refuses to look into the source of this instinct on the extraordinary grounds that physiology is out of bounds for a psychologist—even a medical one. He outlines by simple steps the chain of logic by which freudians are convinced that the first instinct of life is a striving for death.

In presenting Freud's theory of the neuroses, he neatly straddles the problem of the proportion of influence between heredity and environment by conceiving an "innate sexual constitution" as a congenital factor, and visualizing accidental psychic traumas as the acquired elements. By the usual legerdemain of freudian logic, a neurotic symptom may be at once a self-chastisement and a self-gratification, and the wandering uterus of Plato's hysteric is replaced by a wandering libido of Freud's.

The author warns one not to be hasty in judging psychoanalysis by its results; in this way, the value of suggestion is dismissed, for the stroking hand of the hypnotist becomes a symbol of the tenderness of the mother. Any success that may attend suggestion is ascribed to the fixation of the patient's libido onto the hypnotizer, a method that at once robs the mesmerist of his success and condemns his method. In considering Rivers' concept of a self-preservation instinct, Mitchell, rather than reject it, extends the freudian libido to include it; thus, at one stroke, all the war neuroses are taken into the psychoanalytic fold.

In outlining Jung's hypothesis, the author terms it a "heresy" and treats it as such, begrudging Jung credit for the theory of the racial unconscious. It is this, Mitchell says, that Freud meant by typical dreams. In very neat terms the hypothesis of Freud and his two heretic disciples are contrasted. The purpose of life is pleasure (Freud), adaptation (Jung) or power (Adler).

Psychoanalysis, Mitchell insists, is a science, scientifically arrived at. He airily waives away the objection that this method of discovering psychic facts is subject to the observer's prejudice. He concludes his text with the inevitable

cliché of freudian logic, that he whose subconscious has not been revealed to him by this technic cannot know enough about his mind to criticize the freudian interpretation. Critics of psychoanalysis must indeed take care, for anything they say may be used against them.

The Manic-Depressive Psychosis. By Helge Lundholm. Price, $1. Pp. 86. Durham, N. C.: Duke University Press, 1931.

A Norwegian psychologist, for years connected with the McLean Hospital under Dr. Packard and associated with McDougall's department at Harvard, offers in this first Duke University Psychological Monograph a systematic psychologic formulation and tabulation of his conception of the manic-depressive psychosis. It is somewhat unfortunate that the whole study starts with the fundamental hypothesis of the toxic nature of these disorders, for which there are "no facts." The formulation is adapted to this assumption and is said to corroborate it. The description follows closely McDougall's conception of "sublimation" and "repression" and the basic instincts and the previous articles of the author and leads to tabulations of the probable ways of evolution of the main symptoms and factors, without any correlation with the work of others.

Lundholm sees three fundamental agents at work: (1) a cycloid constitutional temperament, with feelings of increased potency or of inadequacy; (2) the constitutional egotistic trait or E-disposition (in contrast to the altruistic A-disposition), and (3) the basic toxic disintegrative agent, bringing about the state of the synapses to which is referable the majority of the symptoms.

There are three "levels of profundity of disintegration," the initial one a release of the E-disposition through beginning disintegration and a fixation in the mood which by chance is predominant at the onset, under the influence of the predominantly egotistic urge, and often with initial retardation or in extensive exhaustion, "homogeneous retardation." The second level of profundity is marked by a liability to tantrums, sthenic or asthenic, with feelings of omnipotency or inadequacy and corresponding grave judgment defects and delusions.

The third level of profundity of disintegration shows a continual liability to chaotic conflict between nonintegrated disparate impulses and is apt to bring on the third of the three "imperial moods," that of unreality, which is said to account for objective distractibility and to evoke curiosity and inner distractibility or flight and the tendency to misinterpret persons and things, or in case of fear reaction resistiveness and "manipulation folly," the author's term for the patient's feeling the body of others to overcome the feeling of unreality. He has his own definition for "confusion proper" as a never more than momentary deadlock with complete immobility, different from depressive stupor, which is attributed to a gradual exhaustion of the psychomotor effector system of the body.

The study has all the features of a psychologic discourse by one not concerned with the clinical and personal problems presented by the patients. It does, however, give a clear insight into the preoccupations and formulations of the author and the school to which he belongs. As will happen with a formal system, it leads to an appearance of much circular explanation and amplification without getting one much closer to the facts.

The Measurement of the Intelligence of Young Children by an Object-Fitting Test. By Ruth E. Atkins. Price, $1.50. Pp. 81. Minneapolis: University of Minnesota Press, 1931.

Methods of measuring intelligence in young children that require neither language understanding nor language response are of rather recent development and are not altogether satisfactory. Atkins surveys the available tests and concludes that they all require language understanding to some extent. Moreover, many of them suffer from inadequate standardization or poor methods of scoring.

In the object-fitting test, the child need not understand spoken directions or respond verbally. He must select from a group of familiar and interesting objects presented him that one which will fit into the hole in a given papier-maché block. The tasks are graded in difficulty and are suitable for use with children from 2 to 4 or 5. The test has been standardized on 400 children of these ages, so selected that they form a representative sampling of the Minneapolis population. The reliability, determined by the giving of alternate forms, is high. Success with the object-fitting test shows a fairly regular increase with chronologic age. The test was also found to correlate highly with the Minnesota preschool test, a verbal test. There could be no other determination of the validity of the test because outside criteria of intelligence were not available for the preschool children.

It is probable that a variety of tests is advisable for the estimation of intelligence in young children as in other groups, and that no single type of performance is a sufficient index of intelligence. While the object-fitting test should probably not, therefore, be used alone, it is undoubtedly a valuable addition to the intelligence tests for young children. The book includes a manual of directions for the giving and scoring of the test.

Hirnpathologische Beiträge. By Karl Schaffer, Budapest, Hungary, Psychiatrisch-Neurologischen Universitätsklinik, 1931. Volume 10. Pp. 450.

The tenth volume of the "Hirnpathologische Beiträge" from the Psychiatric-Neurological Clinic of the Hungarian University in Budapest, under the direction of Prof. Karl Schaffer, is notable in that it celebrates the completion of twenty years of work in this famous institution. The volume is also dedicated to Prof. S. Ramón y Cajal. There is an introduction by Professor Schaffer, which contains a brief outline of the purpose of the institute, following which is an index of the ten volumes presented up to date, the first volume appearing in 1915. A survey of the contents demonstrates the versatility, wide interests and predominant part played by the director, through whose efforts the institute has been made possible.

The sixteen papers of the tenth volume are divided into three on normal and pathologic anatomy of the cerebellum, six on the histopathology of familial or endogenous diseases, one on the histopathology of the psychoses, one on the histopathology of epidemic encephalitis, two on tumors and three on miscellaneous subjects.

The work of this famous institute compares favorably with that of similar organizations of any other nation and is a credit to the country.

Aphasia in Children. By Dr. Alexander G. Ewing. Price, $3.50. Pp. 152. New York: Oxford University Press, 1930.

In a very brief presentation, the author has made a real contribution to the subject of aphasia in adolescents, for in children in whose cases the diagnosis of aphasia was made he has found that their intelligence, other than auditory, was normal, and that their speech difficulties were consequent to an inability to hear high tones although their hearing for low tones was intact. By means of suitable education he was able to make them speak normally.

The study consists of a careful analysis of the cases of ten such patients and ninety others, consisting of normal children, deaf patients and some adults. Very properly he believes that such children should not be called aphasic, and he terms such difficulties the result of linguistic retardation. He points out that there is no resemblance between the reactions obtained in such children as compared with those in aphasic children, for in the latter, speech difficulties are the result of disintegration of speech functions that had at one time been normally established, while in linguistic retardation speech has never developed.

Altogether it is a stimulating book.

Techniques histologiques de neuropathologie. By Ivan Bertrand. Price, 50 francs. Pp. 375. Paris: Masson & Cie, 1930.

This book fills a much felt need. It brings the subject up to date and includes many methods hitherto only to be found in journals. There are ten chapters: 1. General Procedure; 2. Methods for Cells; 3. Methods for Myelin Sheaths; 4. Methods for Neurofibrils; 5. Methods for Neuroglia; 6. Methods for Microglia and Oligodendroglia; 7. Methods for Connective Tissues; 8. Methods for Products of Degeneration; 9. Methods for Peripheral Nerves; 10. Methods for Bacterial Invasion of the Nervous System.

There is an excellent index not only of the names of those whose methods are given, but also of the histologic and histopathologic elements the demonstration of which forms the subject of the book, such as plaques séniles, syncytium schwannique, microglia. There is an adequate bibliography. The book merits translation into English.

Einführung in die neuere Psychologie. By Emil Saupe. Price, 10 marks. Pp. 426. Osterwieck am Harz, Germany: A. W. Zickfeldt, 1928.

This handbook, in its second and third editions, contains twenty-four articles on as many different fields or tendencies in psychology. Each subject is treated by some prominent investigator in the field. Wertheimer has an article on Gestalt psychology, Adler an article on "individual" psychology, Messer an article on the Würzburg School and another on religious psychology, and Stern an article on "personalistic" psychology. An incomplete but useful bibliography follows each article. The handbook as a whole presents an excellent survey of modern tendencies in psychology in Germany, and is for this reason particularly valuable for the non-German student.

Diagnostic et thérapeutique par le lipiodol. By J. A. Sicard and J. Forestier. Price, 50 francs. Pp. 370. Paris: Masson & Cie, 1928.

This is a rather timely work, for the use of iodized poppy seed oil 40 per cent as a diagnostic measure has been receiving increasing attention. In the present work, the whole subject of iodized oil is discussed not only from the neuropsychiatric standpoint, but from that of the whole body. As indicated in the bibliography, which occupies sixty-five pages, the use of iodized oil has been extended very greatly. Nevertheless, its final status has by no means been settled. This book, however, is useful in that it gives the French point of view.

The Psychology of Insanity. By Bernard Hart, M.D. Fourth edition. Price, $1.25. Pp. 191. New York: The Macmillan Company, 1931.

The fourth edition differs from the preceding in that the advances that have been made in the last few years are summarized in an introduction, and in addition there are explanatory footnotes and a bibliography. The author very wisely has not altered the text, for had he brought it up to date, the whole purpose of this short book would have been destroyed.

Medicine: An Historical Outline. By M. G. Seelig, M.D. Second edition. Price, $3. Pp. 205. Baltimore: Williams & Wilkins Company, 1931.

The second edition of this interesting book contains no additional material. The inception of the book was the desire to put on record eight lectures on medical history given by the author before the students of the (St. Louis) Washington University School of Medicine. It originally appeared in 1924.

The book is exceedingly well written, is of great interest and should be in the hands of every physician. The illustrations are excellent.